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Quality by Design (QbD): A Modern Era in Pharmaceuticals

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ABSTRACT

Quality by design is an essential part of the modern approach to pharmaceutical quality. Quality by design (QbD) is more scientific, risk based, holistic and proactive approach in pharmaceutical development for FDA and pharmaceutical industry in drug development. Quality by Design (QbD) is everything you do to directly to promote, prove safety, efficacy and quality of your product from proof of concept to the point at which costumer are buying on regular basics. This novel concept of QbD promotes industries in understanding product and manufacturing process starting with product development which aims basically building quality in product, not by testing it. A company needs to define desire product performance profile [Target product Profile (TPP), Target Product Quality Profile (TPQP)] and identify critical quality attributed (CQA) under this concept of QBD during designing and development of a product. On the basis of information obtained company can build consistent product quality by monitoring and updating its manufacturing processes. This systematic approach to product development and manufacturing has received a great deal from traditional approach. The purpose of present article is to discuss the concept of pharmaceutical Quality by Design (QbD) and describe how it can be help to ensure pharmaceutical quality.

keywords: quality by Design (QbD), Target Product Profile (TPP), Critical Quality Attributes (CQA), ICH guidelines. Food and Drug Administration (FDA)

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INTRODUCTION

The pharmaceutical industry has been a highly regulated industry for many good reasons in the past but still there is some element of risk to the patients [1].These risks are greatly mitigated with the delivery of medicine at the appropriate purity, potency, delivery rate, and so on. [2.] Pharmaceutical industry started using manufacturing technologies in the beginning of 21st century that have been employed since the 1940s and did not make significant changes in manufacturing process because of high cost and long cycle time needed for the approval. This often resulted in inefficient, overly expensive processes that were ultimately not in the best long-term interests of patients. As a result, the FDA (Food and Drug Administration) and other agencies around the world have embraced a new paradigm for regulation [3]. The ‘‘desired state’’ was to shift manufacturing from being empirical to being more science, engineering, and risk based. [4]. Current and desired state of QbD IS explained briefly in table 1.

The Concepts of Quality by De- sign (QbD) was first introduced by Juran and he is often credited for that [4]. Pharmaceutical QbD is a systematic approach to development that begins with pre-defined object often credited for and emphasizes product and process understanding based on sound science and quality risk management (ICH Q8R2). At the beginning of the 21st century the holistic and systematic approach of QbD was relatively new to the pharmaceutical industry. How- ever, elements of QbD were certainly being applied across the industry long before then.

Table 1- Comparison of the current state to the future desired QbD state.

Aspects	Current state	Desired QbD state
Pharmaceutical development	Empirical: typically unvariate experiments	Systematic: multivariate experiments
Manufacturing process	Locked down: validation on three batches; focus on reproducibility	Adjustable within design space: continuous verification within design space: focus on control strategy.
Process control	In process testing for go/non go; offline analysis	PAT utilization for feedback and feed forward in real time
Product specification	Primary means of quality control; based on batch data	Part of overall quality control strategy; based on product performance
Control strategy	Mainly by intermediate and main testing	Risk based; control shifted upstream; real time release
Lifecycle management	Reactive to problems and OOS; post approval changes needed	Continuous improvement enabled within design space

Figure 1- overview of Quality by design

Characteristics of Successful QbD Program

- Involves product design and process development.
- Risk-based, science based.
- Primary focus is patient safety and product efficacy.
- Business benefits are also drivers.
- Results in improved process understanding.
- Results in improved process capability/robustness.
- Systematic development.
- Holistic – applies to all aspects of development.
- Multivariate – interactions are modeled.
- Provides PAR, design space, or suitable equivalent.
- Requires a significant reduction in regulatory oversight post approval.[5]

REQUIREMENTS FOR SUCCESSFUL IMPLEMENTATION OF QBD PROGRAM:

• All the critical sources of variability are identified and explained.

• Variability is managed by the process, and.

•Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions [6] Major goal of a QbD program is the process understanding,

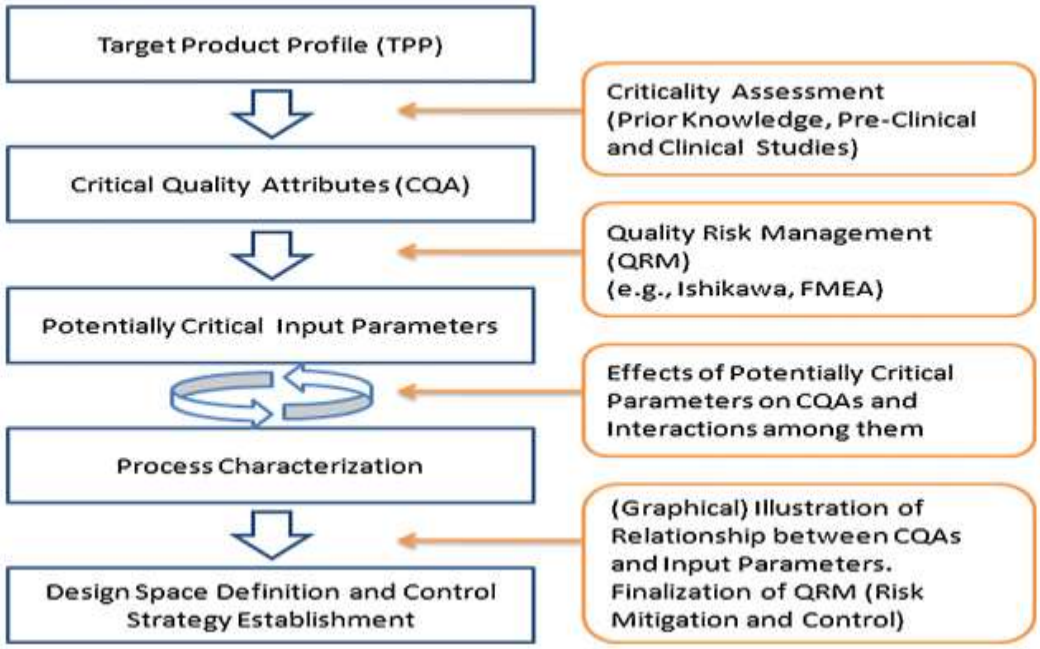

Figure 2- Simplified flow chart of the QbD process

Pharmaceutical quality by testing:

In this system, raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in-process material testing, and end product testing are the processes used to test the quality of final product.[7] The quality of raw material including drug substance and excipients is monitored by testing. For the manufacturing of the product only those excipients and raw materials are used which are having FDA approval or other standards such as USP. [8,9] Finished drug products are tested for quality by assessing whether they meet the manufacturer's proposed and FDA approved specification. If not, they are discarded.[10] Root causes for failure are usually not well understood.

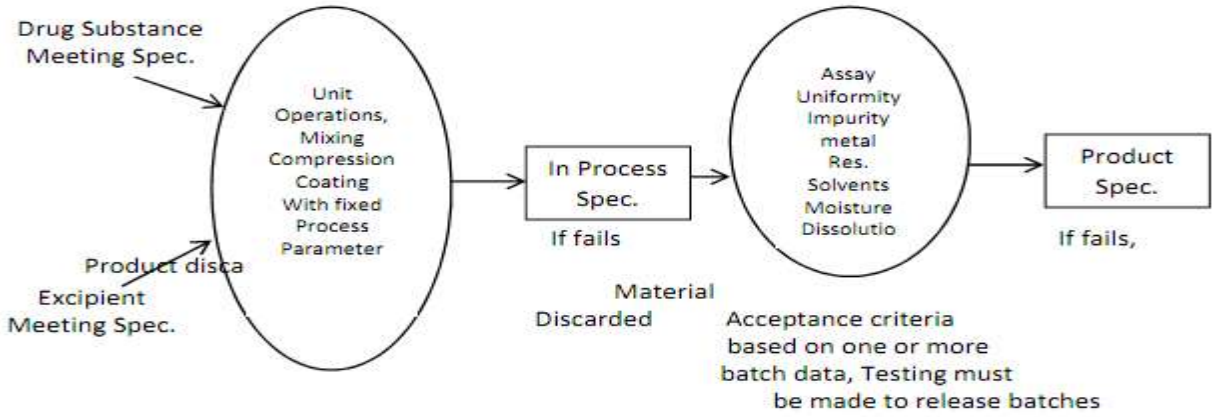

Figure3 – Quality control diagram using QbT.

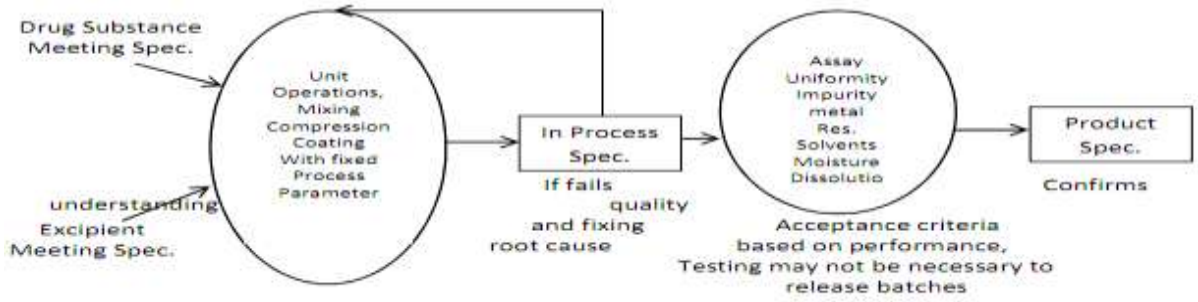

Figure 4- Quality control diagram using QbD.

Steps of QbD program:

Briefly a QbD development process includes stages as described below:

- Use, safety and efficacy of the product are described by the target product profile.
- Formulators and process engineer's use target product quality profile as a quantitative surrogate for aspects of clinical safety and efficacy during product development.
- Drawing together relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use a risk assessment to prioritize knowledge gaps for further investigation.
- Formulation design and identification of the critical material attributes of the final product that must be controlled to meet the target product quality profile.
- Manufacturing process is designed to produce a final product having critical material attributes.
- Critical process parameters and raw material attributes are identified that must be controlled to achieve critical material attributes of the final product.
- Control strategy is established for the entire process that may include input material controls, process controls. The control strategy should encompass expected changes in scale and can be guided by a risk assessment.
- Continuous monitoring and updating of the process to assure consistent quality.[11,12]

Benefits of QbD Program: [13]

- Higher level of assurance of drug product quality is provided.
- Cost savings and efficiency is assured for the pharmaceutical industry.
- Transparency of the sponsor understands the control strategy for the drug product is increased to obtain approval and ultimately commercialize.
- Scale-up, validation and commercialization transparent, rational and predictable are made transparent.

- Innovation for unmet medical needs is facilitated.
- Efficiency of pharmaceutical manufacturing processes is increased and reduction in manufacturing costs and product rejects.
- Minimization or elimination of potential compliance actions, costly penalties, and drug recalls.
- Continual improvement opportunities are created.
- Regulatory oversights are made more efficient.
- Post approval manufacturing changes and regulatory processes are regulated.
- Post approval CGMP inspections are more focused
- First cycle approval opportunities are enhanced.
- Continuous improvement and reduction in the CMC supplement is facilitated.
- quality of CMC is enhanced and reduction in the CMC review time.

QbD and ICH Guidelines:

"Quality by Design" (QbD), is described by several ICH guidelines, including ICH Q8 (R2), ICH Q9 and ICH Q10, and – in its core – focuses on science-based design and development of formulations and manufacturing processes in order to ensure pre-defined product quality objectives.[14] ICH new vision about ensuring product quality is to harmonize pharmaceutical quality system applicable across the life cycle of product emphasizing an integrated approach to quality through science.

1] Pharmaceutical development (Q8):

- Past- Data transfer/ variable output
- Present- Knowledge transfer/ science based/ consistent output.

2] Quality risk management (Q9):

- Past- Used, however poorely defined.
- Present- Apportunity to use structured based thinking.

3] Pharmaceutical quality system (Q10): [15]

- Past- GMP checklist.
- Future-Quality system across the product.

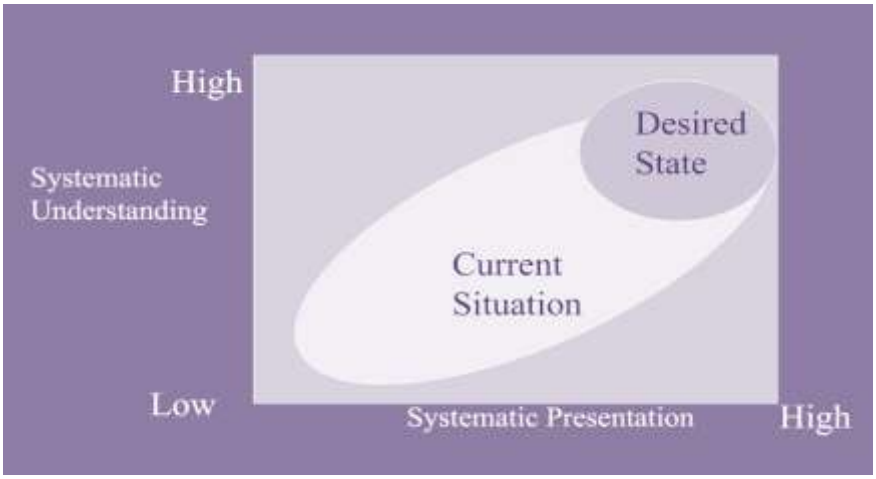

Figure 5- ICH new vision about quality

AILMENTS OF QUALITY BY DESIGN (QBD): [16]

- Quality Target Product Profile (QTPP)
- Critical Quality Attributes (CQA)
- Risk Assessment
- Design Space
- Control Strategy
- Lifecycle Management

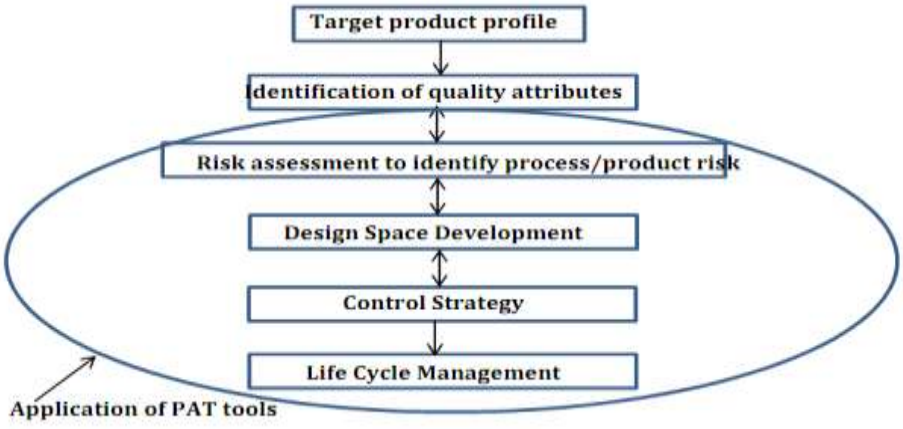

Figure 6- Elements of QbD programme.

1]Quality target product profile: [15,16]

(ICH Q8 (R2)) defines QTPP as a prospective and dynamic 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. The target product quality profile (TPQP) is used to design and optimize a formulation and manufacturing process and considered as a quantitative surrogate for aspects of clinical safety and efficacy .It should include quantitative

targets for impurities and stability, release profiles (dissolution) and other product specific performance requirement and also includes dosage form and route of administration, dosage form strength(s), therapeutic moiety release or delivery and pharmacokinetic characteristics appropriate to the drug product dosage form being developed and drug product-quality criteria (e.g., sterility and purity) appropriate for the intended marketed product. TPP is the novel concept in the QbD paradigm and whose extension is TPQP. Drug product should possess this quality characteristic in order to reproducibly deliver the therapeutic benefit promised in the label. TPQP is important tool used by the formulation scientist to establish formulation strategies and keep formulation efforts focused and efficient. TPQP is related to identity, assay, dosage form, purity, stability in the label. TQPP is both prospective, it is describes the goals for the development team, and dynamic that is the QTPP may be updated or revised at various stages of development. The FDA has published a guidance defining the Target Product Profile (TPP) that focuses on the consumer (patient) and the desired product label. The QTPP is a subset of the TPP and is more oriented towards the chemistry, manufacturing and controls (CMC) aspects of development [17] In table 2 an example is given for the expected TQPP for the given product. The TPP can play a central role in the entire drug discovery and development process such as:

1. Effective optimization of a drug candidate is possible
2. Decision-making within an organization can be done.
3. Design of clinical research strategies, and
4. Constructive communication with regulatory authorities is easy.

Table 2- Quality target product profiles for a lyophilized sterile vial.

Indication	Chronic disease(Treatment of nervous breakdown)
Dosage form	Lyophilization of solution for injection
Dosage strength	Nominal dose 20ng/vial
Administration route	Subcutaneous(0.8ml)
Reconstitution time	Not more than 2 min
Solution for reconstitution	1ml in 0.9ml saline(provided by the pharmacy)
Packing material drug product	2R glass vial, rubber stopper, meets pharmacopoeial requirement for parenteral dosage form
Shelf life	Two year at 2-8^0 C
Drug product quality requirement	Meets pharmacopoeial requirement for parenteral dosage form as well as product specific requirements
Stability during administration	Reconstituted solution is stable for 24h at temperature≤ 30^{0}C

2] Critical quality attributes:

CQAs identification is the next step after TQPP is identified. A CQA has been defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within

an appropriate limit, range, or distributed to ensure the desired product quality" Risk assessment strategy is used for identification of CQA as per the ICH guidance Q9. Key in making risk assessment is prior product knowledge, such as the accumulated laboratory, nonclinical and clinical experience with a specific product-quality attribute is. Data from similar molecules and data from literature references can also be used for knowledge. This information provides a rationale for relating the CQA to product safety and efficacy. The use of robust risk assessment methods for identification of CQAs is novel to the QbD paradigm [18]

3] Risk assessment:

Modernization of the Pharma Industry Quality sys- tem is underway now days, as evident from the recently introduced harmonized guidelines from ICH on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Quality Systems (Q10).At the core of QbD is quality risk management (QRM). This is a systematic and integrated approach for assessment, control, communication and review of risks to the quality of the drug (medicinal) product and the associated manufacturing process across the product lifecycle. A key component of QRM is Quality Risk Assessment (QRA) which is an active tool to identify potential risks related to materials, processes, and/or handling. Subsequent mitigation then comprises adjusting designs and/or changing controls. Notably, QRA is not a single 'tick-box' activity. Rather it is an active component of QRM throughout the product and process lifecycle. This also means that if risks can be lowered, or if risks increase, an associated change in controls would be a logical consequence. Ultimately, if high robustness has been designed into the product and process, i.e. risks are low, leaner control would be justified. The concept of QRM, including QRA, is currently becoming increasingly adopted into pharmaceutical development, manufacturing and life cycle management. Its importance as a ''valuable component of an effective quality system'' has also been recognized. In spite of all the positive experiences from adoption of QRM so far, a recurring comment from implementation is that a weakness of current practices of risk rating in risk assessments is in part subjective. Joint exploration, evaluation/development, and adop- tion of new science based methodologies and practices will be therefore be required which bridge between the technical design parameters of pharmaceutical products and processes and their consequent clinical performance. [19]

4] Design space:

ICH Q8 (R1) defines design space as, the multidimensional combination and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality.[12] The Design Space defines the relationship between Critical Quality

Attributes (CQAs) and Critical Process Parameters (CPPs), and identifies acceptable operating ranges for CPPs. It is the region where acceptable product can be produced. The normal operating range is a subset of the Design Space where routine manufacture is typically performed on a daily basis. Finally, the Control Strategy ensures that operation of the process is maintained within the Design Space. It is intended to prevent operating in regions of limited process knowledge or that are known to cause product failure. Figure shows how these three elements are connected and interact with each other. The Knowledge Space is a summary of all process knowledge obtained during product development. It includes information about critical and non-critical attributes and process parameters. This encompasses the Design Space and normal operating ranges, as well as areas where it is known that unacceptable product is produced. The Knowledge Space only contains information regarding regions that have been investigated, and beyond its boundaries is considered to be unexplored space. [20]

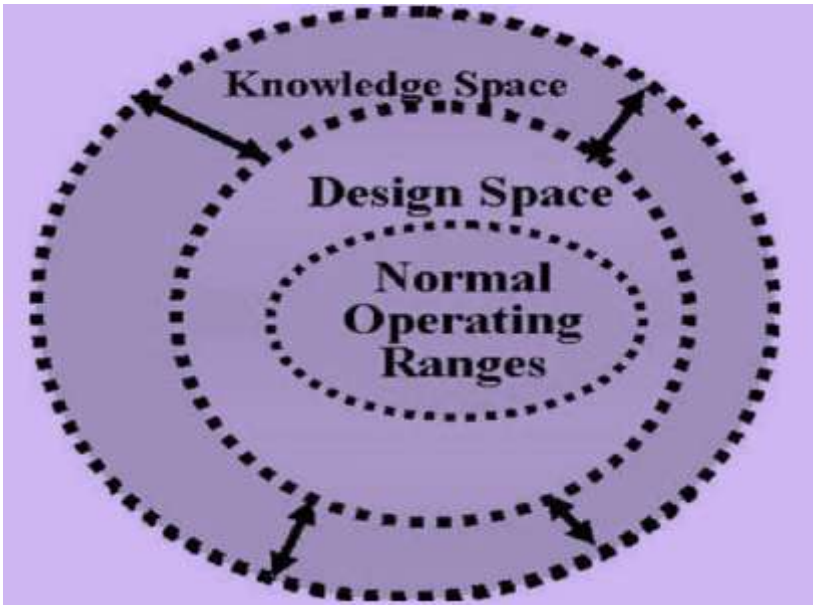

Figure 7- Linkage between knowledge space, design space and normal operating ranges criticality.

5] Control strategy:

Control strategy is defined by ICH(Q8-R1) AS"A planned set of controls, derived from current product and process understanding that ensures process performance and product quality". The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Particularly, the control strategy may include:

- Control of raw material attributes (e.g., drug substance, excipients and primary packaging materials) based on an understanding of their impact on process-ability or product quality.
- Product specifications
- Procedural controls
- Facility controls such as utilities, environmental systems and operating conditions
- Controls for unit operations that have an impact on downstream processing or end-product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution)
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

The Control Strategy should establish the necessary controls based on patient requirements to be applied throughout the whole life cycle from product and process design through to final product, including API and Drug Product manufacture, packaging and distribution [13, 18, 21]

6] Lifecycle assessment:

After approval, CQAs are monitored to ensure that the process is performing within the defined acceptable variability that served as the basis for the filed process design space. The primary benefit of an expanded process design space would be a more flexible approach by regulatory agencies. In the QbD paradigm, process changes within the design space will not require review or approval. Therefore, process improvements during the product life cycle with regard process consistency and throughput could take place with fewer post approval submissions. In addition to regulatory flexibility, the enhanced understanding of the manufacturing process would allow more informed risk assessment as per ICH Q9 regarding the affects of process changes and manufacturing deviations on product quality. Manufacturing experience grows and opportunities for process improvement are identified, the operating space could be revised within the design space without the need for post-approval submission. Over the lifetime of a product, process changes may be required to be made and may require process characterization, validation and filing of the changes to the approved process design space. The quality system needs to provide adequate oversight during QbD implementation of changes that will not go through regulatory approval. Robustness of the quality system would need to be demonstrated with respect to the following four elements: process performance/product quality monitoring;

preventative/corrective action, change management and management review of process performance and product quality [18, 22.]

TOOLS OF QBD PROGRAM:

Design of experimentation, process management methodology and quality risk management are three of the primary tools of QbD. They play a critical role both in development and in the implementation of QbD. They are instrumental in achieving product realization, establishing and maintaining a state of control, and lastly facilitating continual improvement [23.]

- Design of experiments (DOE).
- Process analytical technology (PAT).
- Risk management methodology.

1**] Design of experiments:** Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. DOE is very beneficial because DOE can offer returns that are four to eight times greater than the cost of running the experiments in a fraction of the time. A methodology for designing experiments was proposed by Ronald A. Fisher, in his innovative book

The Design of Experiments (1935).Maximum information can be gained from a minimum number of experiments by applying DOE. Factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness, and friability when DOE is applied in the process. As each unit operation has many input and output variables as well as process parameters, it is impossible to experimentally investigate all of them. Scientists have to use prior knowledge and risk management to identify the key input and output variables and process parameters to be investigated by DOE. DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those who do not, as well as details such as the existence of interactions and synergies between factors.[13,15]

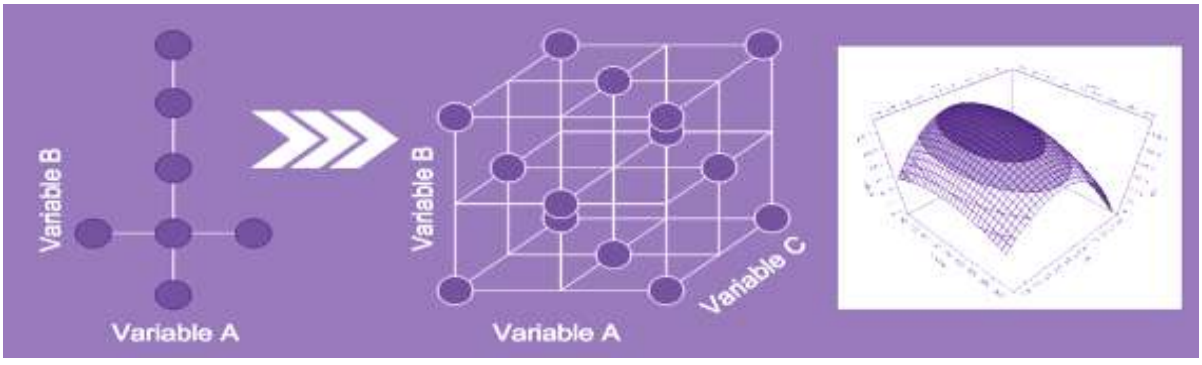

Figure-8 a)Traditional b)Fractional factorial design.

2] Process analytical technology:

"A system for designing, analyzing, and controlling manufacturing through measurements, during processing of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality is defined as process analytical technology (PAT). The main target of PAT is to "enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design." critical process parameters primary focus of on-, in- or at-line PAT applications. In principle, real-time PAT assessments provides the basis for continuous feedback and result in improved process robustness. PAT is useful tool in the RTRT (Real Time Release Testing) as it monitors the particle size, blend uniformity, granulation, content uniformity, polymorphism , dissolution and monitoring the process online, at the line and offline, thus it reduces the release testing of the product [6,24]

3] Risk assessment methodology: A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle is called as quality risk management methodology. Risk assessment is a helpful science-based method, used in the quality risk management that can help in identifying the material attributes and process parameters that potentially have an effect on product CQAs. Risk assessment is typically performed in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. In QbD, the team scientist utilizes risk assessment tools in the R&D lifecycle.

Decision taken based on this technique generally impact the quality and costs attributes to a much greater extent than decisions made during process development and later in the product lifecycle. Risk assessment tools can be used to identify and level parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and primary experimental data. Once the considerable parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding. The pharmaceutical industry and regulators can evaluate and manage risks by using well-known risk management tools and/ or internal procedures such as,

- Basic risk management facilitation methods (flowcharts, check sheets etc.);
- Failure Mode Effects Analysis (FMEA);

- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools [24]

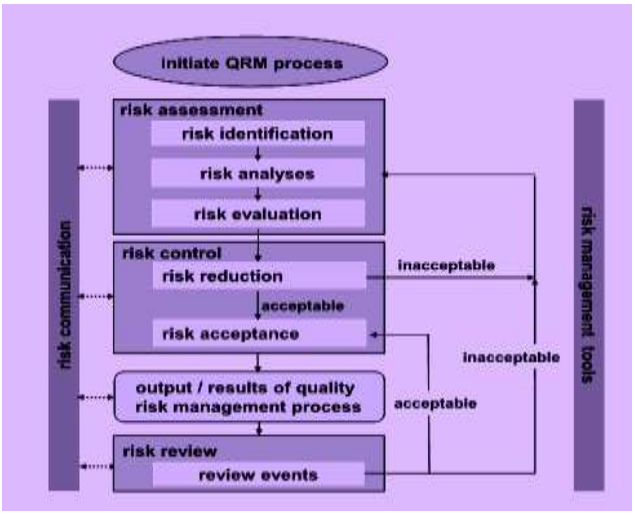

Figure 9- Risk management process according to ICH Q9.

Challenges of implementing Qbd with FDA perspective:

Although QbD is novel and highly beneficial approach in pharmaceuticals still there are some challenges for its implementation,

- Putting new concepts/ approaches into practice (QbD, Design space, Quality risk management)
- Diversity of products.
- Different regulatory processes (NDA, ANDA.BLA)
- Expectation for QbD-based submission while addressing traditional requirement's (dual process) Integration of review and inspection work in progress, Broad spectrum of approaches to development manufacturing, and quality operations across industry implementing, harmonizing Heavy workload and limited resources.
- Implementation challenges to industry includes culture change, information on application, Role of an industry scientist's in regulatory discussions, Business challenges includes removing silos across business units, remove budgeting silos across business

units additional investment during development to achieve efficiency and lower manufacturing cost over Lifecycle, Management Support.

- Unpredictability of treatment of QbD across FDA [25]

CONCLUSION:

Quality by design is an essential part of the modern approach to pharmaceutical quality. The Quality by design project aims to encourage and support quality and to stimulate further thinking about the best ways, to broaden knowledge about best practices in policy. While QbD is most effective when it is employed at a product/process design level, it should also be accomplished in the manufacturing and quality assurance environments. Modern quality system would be critical to support QbD and continuous improvement of pharmaceutical products over their lifecycle. The science of product development and manufacturing for pharmaceutical products is not as advanced as in other industries such as chemicals, aircraft, petroleum, and engineered products, where "Quality by Design" concepts are applied more routinely. Application of QbD principles facilitate development of quality products and their assessment throughout their lifecycle, and ultimately, result in greater patient benefit.

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