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Quality by Design (QbD): Principles, underlying concepts, and regulatory prospects

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ABSTRACT

In the past decades, with substantial growth of pharmaceutical companies and the need in enhancement of quality paradigms, adoption of systematic science based technologies was an inherent demand of regulatory agencies and one such technology is quality by design (QbD). The approved interrelated International Council on Harmonization of Technical Requirements for pharmaceuticals for Human Use guidelines, Q8 (pharmaceutical development), Q9 (quality risk management [QRM]), and Q10 (pharmaceutical quality system) drove the path in successful implementation of QbD. The primary focus of this article is made in delivering the underlying concepts that lead in framing of seven vital elements of QbD. Foremost, the fundamental knowledge essential in setting up a "SMART" objective followed with goal articulation by defining QTPP, detailed understanding of critical material attributes/critical process parameters and essentially screening out few and important key critical quality attributes (CQAs) with citing few examples of drugs, their dependent CQAs and other independent parameters by visualizing the concepts of multiple basic and advanced QRM tools and various experimental designs. A detailed understanding on design space, control strategy, lifecycle development, and continuous improvement are described further. Various myths and potential challenges are addressed with respect to practical grounds. QbD will potentiate regulatory authorities in promising safety of pharmaceuticals thereby acting as an omnipresent tool in drug development lifecycle.

Keywords: Goal articulation, hand-in-hand, omnipresent, potentiate, quality paradigms

INTRODUCTION

The 21st century was believed to serve as an era of drastic development in medical facilities and manufacturing versatile and patient friendly pharmaceuticals for the management of prevailing diseases and improving the quality of sound health across the globe. Similarly, the pharmaceutical industries were involved in drug product development and discovery with a rapid pace until an article published in *The Wall Street Journal* in early September, 2003 reported that *"although pharmaceutical industries has a little secret as it invests in futuristic drugs, yet its manufacturing standards lag far behind the potato chips and laundry soap makers,"*[1] alarmed the state and condition of pharmaceuticals which opened the eyes of regulatory authorities to concern over their assurance for patient safety, efficacy, and quality. The major concern was that the pharmaceutical manufacturing processes are in suboptimal state suffering with problems of larger setbacks and increased hesitation to implement new technologies for quality improvement and reduce the sources of variability of pharmaceutical products in compliance with regulatory requirements and moreover large number of New Drug Applications (NDAs) and Approved NDAs (ANDAs) are mainly focusing on chemistry without proper emphasis on manufacturing protocols.[2]

Thereafter, with the view of proper implementation of quality paradigms into pharmaceuticals and modernizing regulations of manufacturing processes in pharmaceutical industry, an incentive was taken forward by United States Food and Drug Administration (USFDA) ascertaining the vital modifications by its final report "*Pharmaceutical cGMPs for 21st century - A Risk Based Approach*" that was published on September, 2004. The key objectives of the agency are to implement systematic – science based policies and risk based orientation on critical areas of drug product development.[3]

In accordance with the above initiative, a series of regulatory guidelines were constituted and documented soon after by The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) whose process of set up and briefings are enlisted in Figure 1.[4]

The Guidelines Q8, Q9, and Q10 served as interlinked framework in establishing the concept of quality by design (QbD) as an integrated approach in fulfillment of objectives of USFDA in delivering quality enriched and streamlined drug product development with faster improvements and positive scaled up post market reviews. Above all, ICH Q8 primarily focuses on establishing the fundamentals of QbD.[5]

As a result of cGMP regulations, FDA's ultimate aim was to transform its chemistry, manufacturing, and control (CMC) review process into systematic science and risk based drug quality assessment system and thus the concept of QbD was introduced into it.[6]

ICH Guidelines

- ICH Q8 (R2) – Pharmaceutical development.
- ICH Q9 – Quality risk management (QRM).
- ICH Q10 – Pharmaceutical quality system.

Here, Figure 2 gives an idea that the above listed guidelines serves as stringent requirements for maintaining quality of a product and manufacturing processes to achieve desired QbD state.

ICH Q8 (R2) states that "Quality cannot be tested or inspected into a finished product but it has to be built into a product or manufacturing process."[7]

ICH Q9 states that "the evaluation of the risk to quality should be based on scientific knowledge ultimately linking to the protection of the patient and the level of effort, formality and documentation of the QRM process should be commensurate with the level of risk."[8]

ICH Q10 has three main objectives, namely, achieving product realization, establishing, and maintaining a state of control and facilitating continual improvement of drug products. It includes applicable GMPs and describes a comprehensive model for effective pharmaceutical quality system based on ISO quality concepts.[9]

Moreover, ICH Q6A defines quality as "suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity." This definition mainly focuses over control specifications.[10]

Historically, the relationship between product quality and product attributes is not well defined or understood. According to USFDA, for successful implementation of QbD there should be greater understanding of available data and sources of data. A knowledge space may be defined as the complete collection of all product and process variables that can even minutely affect overall product quality. Thus knowledge space can be simply abbreviated as region of operatability of the entire available or explorable database.

ICH Q8 defines design space as "multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality." This is also called as region of interest for successful implementation of optimization procedures. Control space

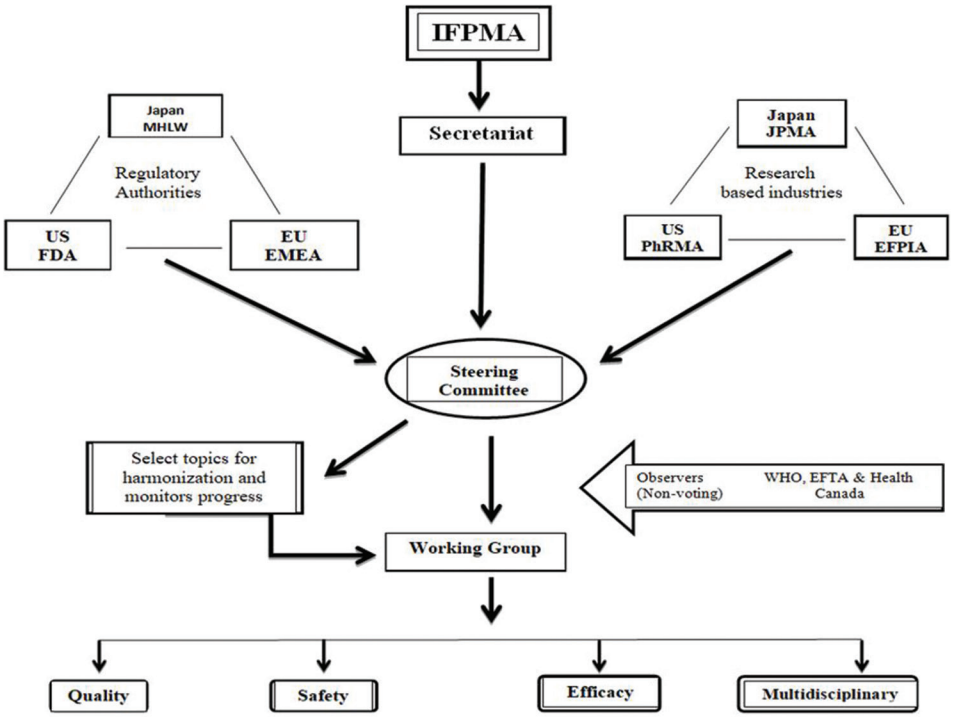

Figure 1: Process of setup of Guidelines by ICH. Abbreviations: IFPMA- International Federation of Pharmaceutical Manufacturers Association., MHLA- Ministry of Health, labour and Welfare, Japan., EU- European Union., JPMA- Japan Pharmaceutical Manufacturers Association., PhRMA- Pharmaceutical Research and Manufacturers of America., EFPIA- European Federation of Pharmaceutical Industries and Associations., EFTA- European Free Trade Association., WHO- World Health Organisation

or operation space is the demarked region of design space for detailed studies of the effects and interactions of refined variables over product optimization.

Historical Aspects of QbD Concept

The present emphasis over quality implementation in pharmaceutical industries can be attributed to fanatical works of Joseph M. Juran, W. Edwards Deming, Dr Kaoru Ishikawa, and Phillip B. Crosby in the field of quality development and assurance. Joseph M. Juran, an American engineer and a pioneer described the fundamentals of quality management in the products and processes with the theories of Juran's triology, stating the objective of pre planning of quality rather than its incidental occurrence through his famous book *"Juran on Quality by Design"* in the early 1970s.[11] According to Juran, quality in a product may be simply defined by two terms, "product features that meet customer satisfaction" and "freedom from deficiencies."[12] Figure 3 illustrates the concept of Juran's triology.

Quality planning involves construction and development of products and processes to meet customer needs. Quality control involves comparison, evaluation, and identification of quality performance and goals. Quality improvement is the process of increasing the quality performance up to the customer satisfaction and needs.

The other principle, namely, Six Sigma was another such historical concept that served as roots in successful implementation of QbD. William Bill Smith and Dr. Mikel J. Harry of Motorola Company, collaboratively developed the concept of Six Sigma in 1986, with the aim of eliminating the chances of defects in a production system down to a 3.4 per million cycles. It uses DMAIC cycle (Define, Measure, Analyze, Improve or Design, Control) to look forward in achieving its goals and it is illustrated in Figure 4.[13]

Comparison between Traditional Approach of Quality by Testing (QbT) and Modern QbD

Traditional regulatory evaluation system involves assessment of product quality and performance by restricting flexibility in manufacturing processes and by end product testing. Thus, QbT approach mainly involves considering all product parameters equally resulting in more review time for low risk products and taking away necessary resources from high risk products.[14] Table 1 describes the comparison between traditional QbT approach and systematic QbD approach.[15]

QBD METHODOLOGY

In the process of ascertaining the concept of QbD, the first objective is to understand the meaning of quality. Janet Woodcock, MD, Deputy Commissioner for Operations/Chief Medical Officer at FDA defined pharmaceutical quality as a product free of contamination and reproducibly delivering therapeutic benefit promised in the label to the customer.[16] ICH Q8 defines QbD 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 QRM."

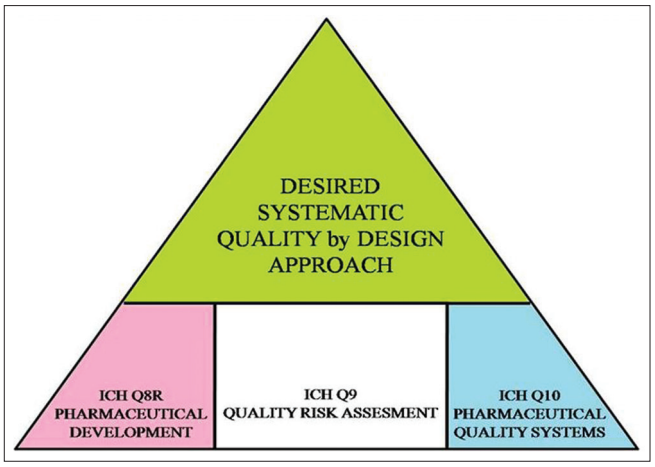

Figure 2: Correlation of ICH guidelines and QbD

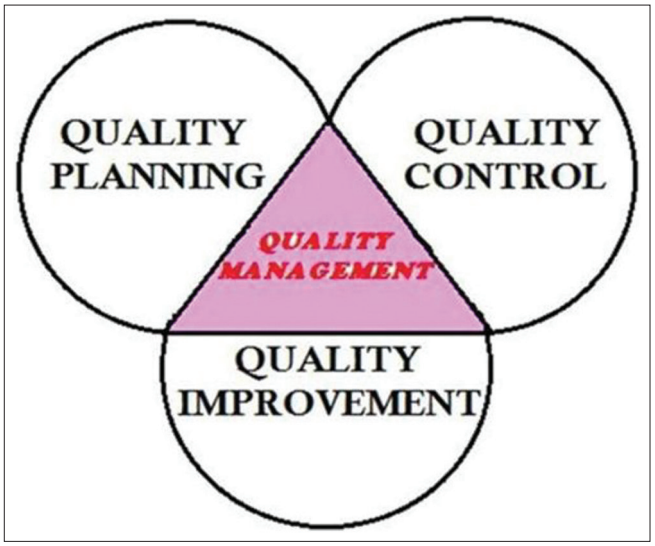

Figure 3: Juran's Quality Triology

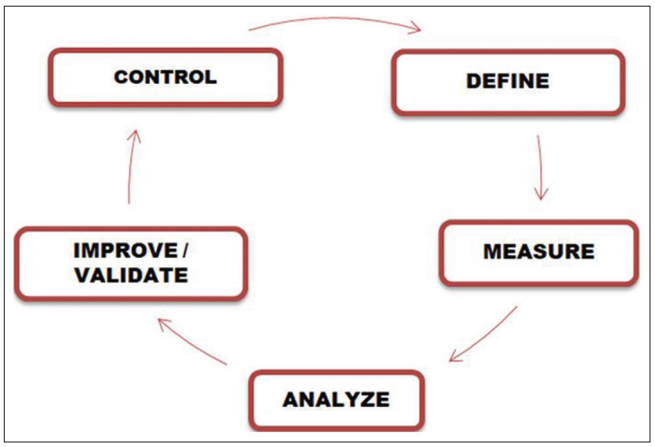

Figure 4: Define Measure Analyze Improve Control (DMAIC) cycle

USFDA states that QbD means designing and developing manufacturing processes during product development stage to consistently ensure a predefined product quality, safety, and efficacy at the end of manufacturing process.[17] Pharmaceutical

Table 1: Comparison between traditional quality by testing approach and systematic quality by design approach

S. No	Quality by testing	Quality by design
1.	Quality is assured by testing and inspection from time to time.	Quality is built into the product by systematic process design.
2.	Process development is empirical with univariate experiments.	Involves systematic process development with multivariate experiments
3.	Manufacturing process is fixed and new changes cannot be implemented easily.	Manufacturing process can be adjustable within design space mainly focusing on the control strategy with continuous verification.
4.	The process mainly focuses on reproducibility disregarding variability.	The process mainly focuses to achieve robustness by understanding and controlling the variability.
5.	Function based designs resulting in process delay and recycling.	Decisions are team based enhancing easy product commercialization.
6.	In process quality control is generally employed for process control and analysis.	Process analytical technology (PAT) is mainly employed for process control and feedback.
7.	Data intensive submission – disjointed information without having "big picture."	Knowledge rich submission – showing product knowledge and process understanding
8.	Design space is not well defined and process is carried out in narrow operating ranges.	Design space is well defined for preeminent product quality.
9.	Product specification mainly depends on data obtained from small batches and is attributed to future batches.	Product performance mainly decides the product specification.
10.	Retrospective quality testing: Each batch has to be tested against the product specification to ensure quality and manufacturing consistency.	Real time quality testing: Process control provides sufficient evidences that the batches will meet specification if tested allowing real-time release of batches.
11.	Need post approval changes for any process improvements made in regard to lifecycle management. Reactive to problems and quality overall summary (QOS).	Any modifications are done generally by continual improvement in design space which does not necessitate a post-approval change.
12.	Regulatory data mainly involves product characterization and process description.	Regulatory data mainly distinguishes how the material attributes and process parameters influence critical quality attributes and how they were modified during manufacturing.

QbD ensures that a product is designed to meet its desired clinical performance and a process is designed to consistently deliver a product that meets its quality attributes necessary for clinical performance.

QbD methodology tends to identify multiple attributes that are critical to quality and need to be present in drug product (both drug substance and excipient attributes), from viewpoint of end-consumer health (or patient health) and establishes how various process parameters can be altered and modified with thorough knowledge on different sources of variability and consequently adapting to implement a reliable, adjustable, and robust manufacturing process to produce a consistent drug product with desired characteristics over time.[18]

To attain the quality enriched drug product, there are seven steps or vital elements explaining the process that are involved in QbD methodology. Figure 5 provides a step-wise representation of vital elements of QbD.

Figure 5: Step-wise representation of vital elements of QbD methodology

Gaining Pre-knowledge over Formulation and Establishing "SMART" Objectives

Knowledge management being one of the key enabler of QbD, greatly emphasizes on serving as a systematic approach in gathering, analyzing, storing, and disseminating information regarding pre-product, pre-process, and various components related to product and processes helping with making it a much transparent and sophisticated essential for product development to market distribution cycle. Prior knowledge can be gathered from drug substances used in the previous product and process development projects, the studies involving different factors influencing drug-excipient interactions, variability of physicochemical and functional properties of excipients, manufacturing processes, analytical techniques used for testing of related dosage forms including its deviations, various

published scientific literatures, and standard pharmacopeias'. Prior knowledge gives a brief understanding in reorganization of various issues or problems that may be occurred and needs to be handled consequently driving the path for making decisions and setting up objectives of work.[18]

Setting up an objective is one of the essential steps before planning or designing a work. The objective should be based on the sources that are available (e.g., a specific and stable polymer to be used in formulation, whether it is available or not), various process equipment and ranges of its operability and so on. It even needs to be "SMART" in action, that is, specific, measurable, attainable, realistic, and time-based. A clearly defined objective helps the team to get focused and include number of requisite skills thus helping in establishment of a complete profile for strategic groundwork in drug development by keeping in account the final stage of finished product market supply.[19]

Articulation of Goals for Drug Product by Defining Quality Target Product Profile (QTPP)

QTPP is also referred as Pharmaceutical Target Product Profile by International Society of Pharmaceutical Engineers (ISPE) Product Quality Lifecycle Implementation (PQLI). On the basis of design for the development of a pharmaceutical product or its manufacturing process, the QTPP acts as an essential surrogate for the aspects of clinical safety and efficacy.[20] Initially, the pharmaceutical companies construct Target Product Profile (TPP) and it is further used to obtain a proper set of objectives by designing QTPP. Target product profile provides a statement of overall intent of drug development program and gives information of drug at a particular stage of development in terms of labeling concepts. The TPP is an excellent tool for defining product specifications to some extent before the product is developed as well as can act as discussion system between sponsor and FDA during entire drug development process, for example,, to establish TPP of a generic drug, one can obtain necessary information from the scientific literature, pharmacopeias, and from Reference Listed Drugs.[21]

Typical sections widely described in QTPP include,

1. Description, Indications, Usage, Dosage, Administration, Dosage Forms, and Strengths.
2. Drug Interactions, Contraindications, over dosage, Warnings, and Precautions.
3. Use in Specific Populations, Patient Counseling Information.
4. Clinical Studies, Clinical Pharmacology, Nonclinical Toxicology, Drug Abuse.

Analytical Target Profile (ATP)

ATP may be defined as analytical criteria necessary to achieve equivalent or better analytical performance. It provides greater flexibility to improve and to develop new analytical methods.

Identifying Critical Material Attributes (CMAs)/Critical Process Parameters (CPPs) and Prioritizing Essential Critical Quality Attributes (CQAs)

The ICH Q8 (R1) defines CQAs as physical, chemical, or microbiological properties or characteristics that need to be controlled either directly or indirectly within an appropriate limit, range, or distribution to ensure the desired product quality (as per the report of ISPE PQLI).[7] CQAs are an essential aspect of manufacturing control strategy and should be identified in Stage 1 of process validation: process design. During this stage, acceptable limits, baselines, and data collection and measurement protocols should be established. CQA is used to describe both aspects of product performance and determinants of product performance since it have been used to describe elements of TPP (e.g., dissolution) as well as to describe mechanistic factors (e.g., particle size, and hardness). CQA is generally assumed to be an attribute of the final product, but it is also possible to indicate a CQA of an intermediate or a raw material. Although many people have identified dissolution as a critical quality attribute, we consider that a set of CMAs that are independent of each other provide specific goals with which to evaluate a manufacturing process. Differentiating the properties of CMAs and multi-faceted performance tests is part of the movement away from QbT to QbD because independent CMAs are the best way to provide a mechanistic link of the product quality to the CPPs in the manufacturing process.

Material attributes (MAs) are any characteristic physical, chemical, or microbiological property of input or output material involved in product quality and performance development. CMAs are the fundamental properties that can be directly linked to the raw materials and manufacturing processes providing a mechanistic link between CPPs and product quality in the manufacturing process. One should differentiate between performance tests of products and CMA to reach the desired state of QbD.

Process Parameter

A process parameter can be defined as any measurable input or output process state variable of the process step within potential operating space (POS) that may or may not influence the desired product quality or consistency. Process parameters may include equipment types, settings, and other operating or environmental conditions.

Different types of process parameters are as follows:

Unclassified process parameters (UPP) are the entire set of many material attributes and process parameters that are identified during developmental process and are important to product quality, but it is of little value to define all parameters as critical because the criticality of an unclassified process parameter is undetermined or unknown. These serve as beginning which may later be subsequently classified as critical or non-CPPs depending on data obtained from experimenters. CPPs is the most influential process parameter, which on modification can cause failure of product in POS and considerable interactions in proven acceptable region (PAR) leading to incompliance with the QTPP. Non-critical process parameters (NCPP) are the process parameter that does not show any failure within POS or interaction within PAR on a realistic change. This can be considered to have a less influential effect over product quality.

Ultimately, we can classify the process parameters into three types depending on their influence over product quality

and performance. Figure 6 classifies different types of process parameters.

The ability of manufacturing processes to tolerate the expected variability of raw materials, process equipment, operating conditions, human, and environmental errors is referred to as robustness. POS may be defined as the identified range of interest within the operating space representing a region between maximum and minimum value of interest of a sponsor to each process parameter. Proven acceptable range is the body of experimental data from the prior knowledge over selected parameter tolerances, showing that operating within these limits leads to acceptable quality. An experimenter can choose a POS larger than or equivalent to the PAR depending on desired sensitivity and quality requirements. Figure 7 gives an overview on POS and PAR.

CMA or Process Critical Control Points (PCCP) and CPP have a high influence over scale up process.[22] Process – Robustness studies are used to demonstrate the effects of variations in process parameters and CMA over product quality and performance.

Process Capability

The process can be well defined and understood by the relationship between CQA and various sources of variation in manufacturing processes. Process understanding should be capable to describe how sources of variation (x) influence the performance of CQA (y) and develop necessary strategies to control these variations as a part of quality control.

$$y=f(x)$$

Above equation shows CQAs as a function of source variations. In general, input parameters will be the principal sources of variation and they may mainly include material, process, equipment, measurement, environment, and human variations.

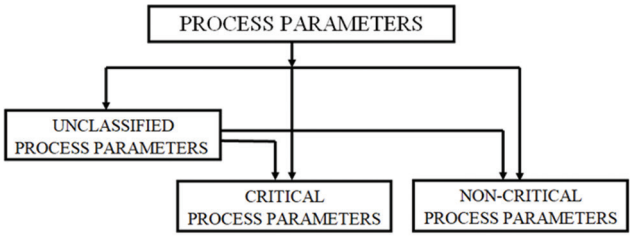

Figure 6: Classification of different types of process parameters

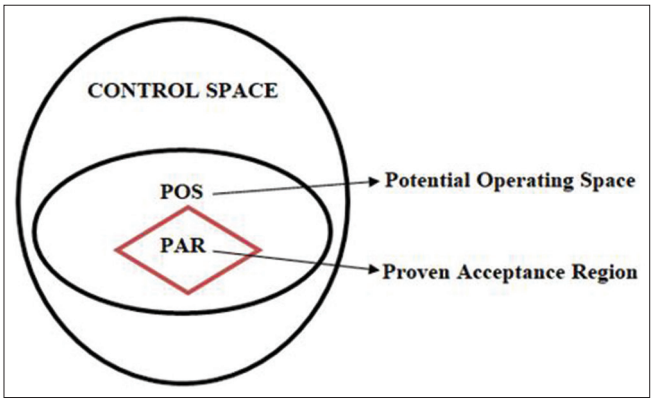

Figure 7: Potential Operating Space (POS) and Proven Acceptable Region (PAR) under control space

Hence, we can describe total process variation as the function of all source variations which can be measured by variance or standard deviation (σ) of average batch data.[23]

$$=f(\sigma\ material+\ \sigma\ process+\sigma\ equipment+\ \sigma\ measurement+\ \sigma\ environment+\ \sigma\ human)$$

ICH Q10 defines process capability as "ability of a process to realize a product that will fulfill the requirements of that product." Process capability may be defined as a statistical measure of inherent process variability to demonstrate the reproducibility and process consistency.

Process capability is indicated by Process Capability Index or Taguchi Capability Index. It is a Six Sigma formula indicating the ratio between value of tolerance for a particular characteristic and process capability.[24]

$$Process\ capability\ index\ (CpK) = \frac{Allowable\ Process\ Spread}{Actual\ Process\ Spread}$$

$$Process\ capability\ index\ (CpK) = \frac{USL - LSL}{6\ \sigma}$$

Where "*USL*" denotes upper specification limit and "*LSL*" denotes lower specification limit and Figure 8 illustrates a graph indicating *LSL* and *USL*. "σ" is the measure of standard deviation. A process is regarded capable if *CpK* is greater than one and is deemed to be operating at a high variation if *CpK* is less than or near to zero.[25] Table 2 illustrates examples of different drugs, their key CQAs and independent variables.[26-48]

Process Analytical Technology (PAT)

The effects of CPPs on final product are complex to estimate and QbD acts as a deliberate tool in optimizing the manufacturing process using process analytical technology. PAT is defined as an integral part of QbD, where even if the complex interplay of process change and impact cannot be predicted, at least it allows in extended monitoring, testing, analyzing, and adjusting the manufacturing processes to completely control

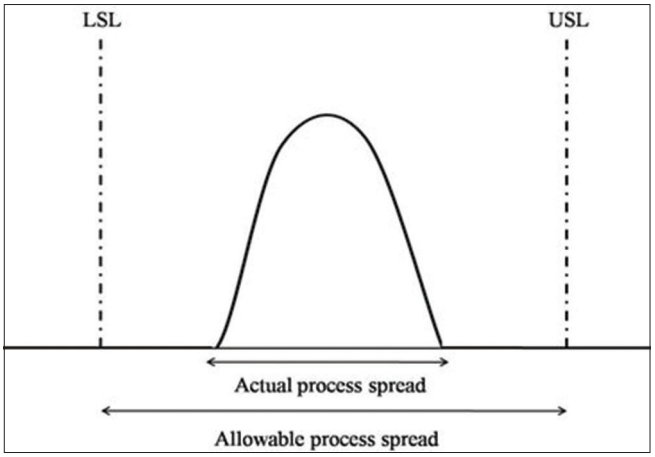

Figure 8: Graph indicating Lower Specification Limit (LSL) and Upper Specification Limit (USL)

Table 2: Examples of different drugs, their key CQAs and independent variables

Sr. No.	Drug	Dosage form	Critical quality attributes (CQAS)	Independent variables
1.	Lacidipine[26]	Liposomes as nanocarriers.	Particle size, solubilization efficiency, *in vitro* drug release.	Ratio of Cetylalcohol to Tween® 80 and ratio of drug to the excipient mixture.
2.	Ibuprofen[27]	Mannitol based Orodispersible tablets.	Hardness, disintegration time, porosity	Tablet diameter and Compression force (CF)
3.	Gentisin[28]	Nanostructured lipid carriers (NLC)	mean particle size, polydispersity index, zeta potential, encapsulation efficiency	Drug concentration, Gelucire 44/14 concentration in total solid lipid, liquid lipid concentration, and surfactant concentration
4.	Camptothecin[29]	Mannitol coupled Camptothecin Nanoparticles (CP-NPs)	Drug loading efficiency, particle size, polydispersity index.	Percentage of Camptothecin in Camptothecin and mannitol combination, concentration of Camptothecin in working liquid, number of homogenization cycles, homogenizer pressure.
5.	Baicalin[30]	Solid lipid Nanoparticles	Entrapment efficiency, particle size, polydispersity index.	Amount of drug, drug to lipid ratio
6.	Ranitidine HydroChloride[31]	Floating asymmetric membrane capsule	Cumulative percentage drug release	levels of membrane former, pore former, and osmogen
7.	Chloramphenicol[32]	Solid lipid nanoparticle	Entrapment efficiency, drug loading, turbidity.	Amount of solid lipid, amount of surfactant, and drug/lipid ratio.
8.	Valsartan[33]	Self-nanoemulsifying drug delivery systems (SNEDDS)	Self-emulsification time, percentage drug release for 15 min, globule size	Amount of capmul, amount of Labrasol, amount of Tween 20.
9.	Felodipine[34]	Drug solid mixture with hydrophilic carriers and polymeric surfactants.	Maximum solubility, equilibrium solubility, dissolution efficiency.	Amount of Hydroxypropyl methyl cellulose, amount of polymeric surfactants Inutec®SP1, amount of Pluronic®F-127 and preparation techniques, physical mixture (PM) or solvent evaporation (SE)
10	Metformin[35]	Dual Mechanism Gastrofloatable and Gastroadhesive Delivery System	Mean dissolution time, Gastro adhesive strength.	Amounts of alginate, pectin, polyacrylic acid (PAA), and poly lactic-coglycolic Acid (PLGA).
11.	Vancomycin[36]	Nanoparticles	Nanoparticle size, encapsulation efficiency	chitosan concentration, chitosan/tripolyphosphate mass ratio, vancomycin/chitosan mass ratio
12.	Tamoxifen[37]	lecithin organogel (LO)	Viscosity, Gel strength, Spreadability and Consistency index	Type and amount of Phospholipid, Poloxamer™, Auxillary Gelators, and Organic solvent.
13.	Diclofenac epolamine[38]	Poloxamer Microemulsion based gel (PMBG)	Maximum amount of oil, Minimum globule size, Optimum drug solubility.	Amount of the oil phase (Capryol®), amount of the Smix (a mixture of Labrasol®/Transcutol®, 1:2 w/w) and amount of water.
14.	Stearoyl-gemcitabine[39]	polymeric micelles	Particle size, Encapsulation efficiency, sustained release behavior of the drug.	Initial drug/polymer ratio, Total solid content, and the type of organic solvent
15.	Glicazide[40]	Self-emulsifying drug delivery systems (SEDDS)	Particle size	Oil (Capryol 90), surfactant (Cremophor EL), cosurfactant (Akoline MCM)
16.	Terbinafine[41]	Microemulsion-Based Gel	Globule size	amount of oil, Smix (mixture of surfactant and cosurfactant), water.
17.	Insulin[42]	Nanoparticles	size, zeta potential, polydispersity index, entrapment efficiency	pH of polymer solution, concentration ratio of polymer/insulin, polymer type
18.	Itraconazole[43]	Micro emulsions	Drug loading, globule size	Amounts of oil, s-mix, water
19.	5-Aminosalicylic acid (5-ASA)[44]	Pellets	pellet yield, fine, and coarse mass fractions, mean particle size, distribution width, particle shape, bulk density, mechanical resistance, dissolution behavior (MDT).	5-ASA:MCC ratio, PVP, and water content of pastes, extrusion speed and spheronization time
20.	Naproxen[45]	Pellets	Quality of the pellets	Spheronization speed, spheronization time, extrusion speed, drying method, CCMC-Na concentration, lactose concentration, water concentration, and Tween 80 concentration

(Contd...)

Table 2: *(Continued)*

Sr. No.	Drug	Dosage form	Critical quality attributes (CQAS)	Independent variables
21.	Carbamazepine[46]	Elementary osmotic pump	Release rate, Release kinetics.	Plasticizer type, amount of plasticizer, semi-permeable membrane (SPM) thickness, orifice size.
22.	Celecoxib[47]	Drug loaded PLGA Nanoparticles	Size of nanoparticles, drug release	PLGA content, surfactant concentration, organic phase volume
23.	Gemcitabine[48]	Drug loaded Bovine serum albumin nanocarrier preparation.	Size of nanoparticles, zeta potential, entrapment efficiency.	BSA concentration (% w/v), volume of BSA solution to total ethanol ratio (v : v), concentration of diluted ethanolic aqueous solution (% v/v)

and improves efficiency of drug product. Figure 9 illustrates PAT and its ease of optimization of product quality as in case of pre-product optimization, different critical attributes, and parameters is difficult to predict but with sound scientific knowledge they can be easily fixed whereas in case of post-product optimization, the quality is hampered and it becomes costlier to be fixed as entire product development is completed.

QRM

"Risk" is defined as "the effect of uncertainty on objectives."[49] ICH Q9 defines QRM as a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle. QRM is the structural tool of QbD for systematic risk assessment of all possible sources of variation to sort out highest ranking risk factors from large pool of input variables.

Risk assessment involves association of CQAs and process performance attributes with process input variables for proper assessment and control of manufacturing risks by screening out important and necessary "CMAs/ CPPs" out of specious "so many"[50] and ranking them based on severity of risk, that is, low risk , modern risk, and high risk.[51] Figure 10 outlines the flow chart of overall QRM.

International Standards Organization (ISO)[52]

ISO 31000:2009 published in November 2009 is considered to be the family of standards associated with the risk management. It is developed such that risk management principles are applicable to all firms and operations concerned with the risk management. These guidelines have life time applicability over concerned operations of any nature and having either positive or negative consequences.

ISO 31000 families includes:

1. ISO 31000:2009 Risk Management principles and guidelines.
2. ISO 31010:2009 Risk Assessment Techniques.

ISO 31000 provides certain key factors for successful implementation of QRM in accordance with QbD, they include:

1. It ought to be the integral part of organizational process.
2. It should be well tailored taking account of best available information.
3. It must be a part of decision-making.
4. It has to address uncertainty by taking human errors into consideration.

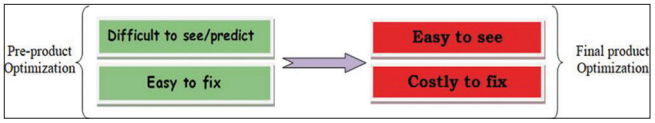

Figure 9: Consequences of pre- and post- optimization of drug products

5. It must be systematic, structured, transparent, and inclusive.
6. It has to be dynamic, iterative, and responsive to change for continual improvement and enhancement.

Figure 11 demonstrates the steps involved in QRM and Figure 12 describes the processes involved in risk assessment (step - 1 of QRM).

Tools of Quality Risk Management

A competent quality management system utilizes proactive risk assessment tools for providing risk and science based reviews to aid in identification and control of quality issues.

Basic risk assessment tools

The differences between various basic risk assessment tools are described in Figure 13.

Note: Other basic risk assessment tools include: Check sheets and control charts.

Advanced risk assessment tools

Different types of risk assessment tools with their description and potential areas of application are outlined under Table 3.

Experimental Designs

Different types of experimental designs are classified under Figure 14 and a brief description on optimization designs/ response surface designs and screening designs is presented in Figures 15 and 16.

DESIGN SPACE[71]

ICH Q8 (R2) defines design space as "The multidimensional combination of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality." Design space describes the relationship between process inputs and CQAs. According to the ICH initiatives, working within a design space does not necessitates post approval changes, so submitting appropriate design space to FDA (by the applicant) is a pathway to work under it, without any further regulatory assessment or approval. Movement

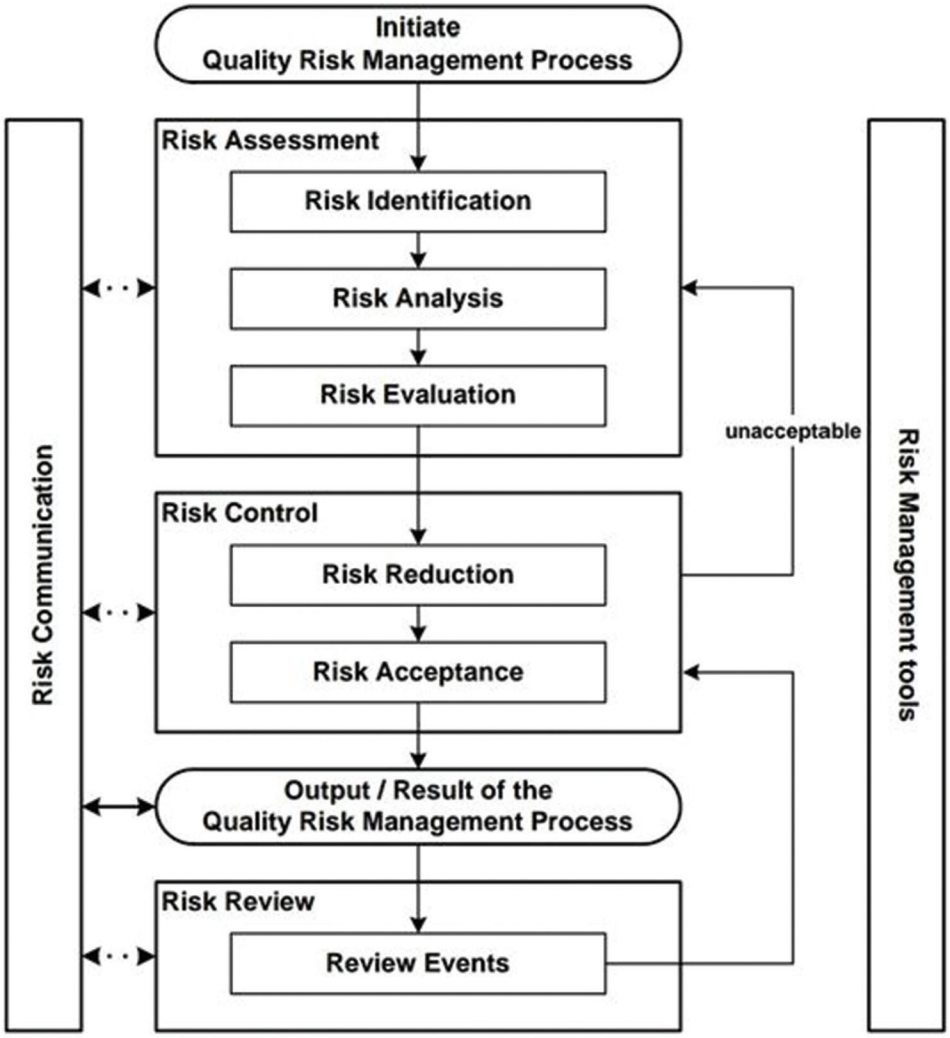

Figure 10: Outlining the overall Quality Risk Management process. (*ICH Harmonized Tripartite Guideline Q9- Quality Risk Management, 2005*)

Step 1: **Risk Assessment:** Risk assessment involves identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. (Figure)	**1. Risk Identification:** Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. **2. Risk Analysis:** Risk analysis is the qualitative or quantitative estimation of the risk associated with the identified hazards. Qualitative risk assessment is represented in numerical probability where as Quantitative risk assessment is represented with terms high, medium and low. Quantitative risk assessment is suitable for one consequence at one time. **3. Risk Evaluation:** Risk evaluation compares the identified and analyzed risk against given risk criteria.
Step 2: **Risk Control:** Risk control includes decision making to reduce and/or accept risks to a predetermined acceptable level. Risk Reduction and Risk Acceptance are the major parts of risk control.	**1. Risk Reduction:** Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. **2. Risk Acceptance:** Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified
Step 3: **Risk Review:**	The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Risk review involves meticulous check of results of risk assessment and risk control to make further improvements in Quality Risk Management (QRM) protocols. Risk review may include reconsideration of risk acceptance decisions.
Step 4: **Risk communication:**	Risk communication involves the sharing quality risk management data between experimenters, sponsors and other parties. Risk management data should be strictly submitted for each and every risk at the end.

Figure 11: Description of steps involved in Quality Risk Management

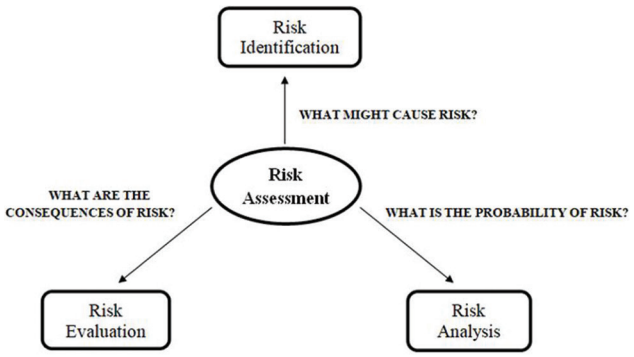

Figure 12: Processes involved in Risk Assessment (step-1 of QRM)

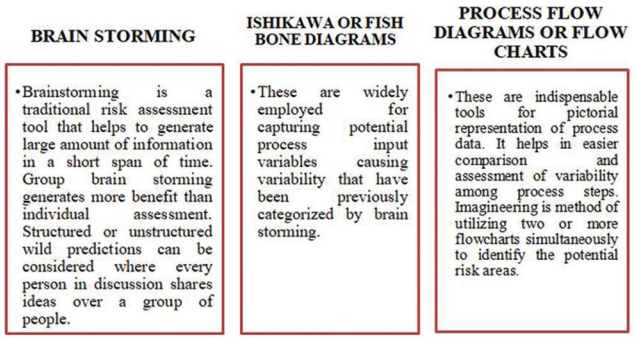

Figure 13: Comparison between different basic risk assessment tools

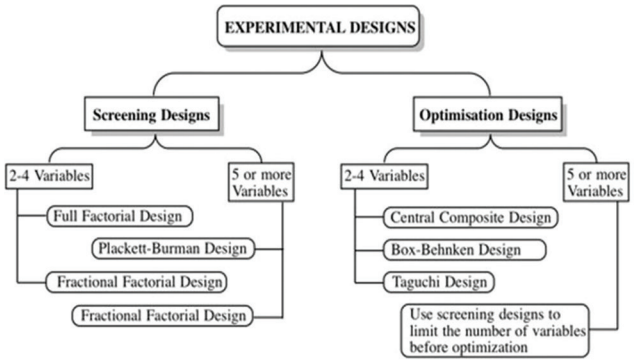

Figure 14: Classification of different types of experimental designs

outside the design space is normally considered to be a change and would initiate a post-approval change process. It should be noted that design space and QbD are not transposable terms. Design space is not a checkbox requirement for successful implementation of QbD. The product and process knowledge can be successfully obtained and implemented even if there is no formal establishment of design space. An overview on design space is shown in Figure 17.

Design space should provide knowledge of all product and process variables and their impact over CQAs across several unit operations involved in product manufacturing. In other words, the design space should give complete information about the proven acceptable ranges of all CPPs along with their associated CQAs. In general, design space would be equipment and scale up dependent depicting greater variations across

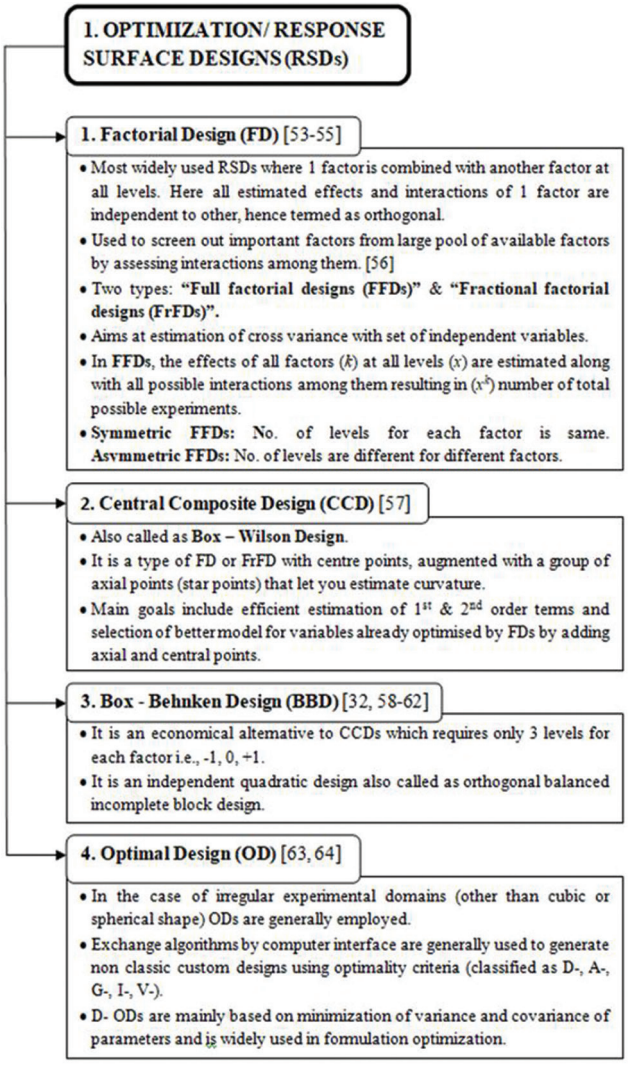

Figure 15: Brief description of different types of optimization/ response surface designs

laboratory and commercial scale. Design space is usually established by conducting multivariate analysis between CQAs and CPPs using appropriate design of experiments. If multiple CQAs are influenced by more number of same CPPs, the acceptable operating region may be greatly limited. Product conceptualization and identification of appropriate QTPP are the essential aspect of the development of design space. CQAs, CPPs, and their interactions for construction of design space are identified by prior knowledge and preliminary risk assessment along with a variety of multivariate or multifactorial models and experimental designs. Risk assessment and process development experiments should reveal link between input variables and CQAs. This will help in selection of variables to be included in design space and establishment of range of variables that ensure consistent product quality. Proven acceptable ranges derived from univariate experimentation data provide necessary knowledge in construction of a design space. During development of design space to existing products multivariate models can be employed for retrospective evaluation of historical production data.

Design space depicts normal operating ranges over a pharmaceutical quality system and other operating ranges

Table 3: Different types of risk assessment tools with their description and potential areas of application

S. No.	Types of risk assessment tools	Description	Potential areas of application
1.	Failure Mode Effects Analysis (FMEA)	It provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance relying on product and process understanding for methodical reduction in analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures. It is handy to access potential degree of risk for every operating parameter and analyze the impact of these parameters on overall product performance. It mainly involves the assessment of severity, occurrence, and detection.	Applicable to prioritize and evaluate risks associated with equipments and facilities.
2.	Failure Mode, Effects and Criticality Analysis (FMECA)	FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their delectability, thereby becoming a Failure Mode Effect and Criticality Analysis.	Applicable for risk ranking of each failure mode or risk associated with manufacturing processes in pharmaceutical industry.
3.	Fault Tree Analysis (FTA)	The FTA tool is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or sub-system) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.	Provides visual representation of failure modes and multiple factor effects indicating the root cause of failure.
4.	Hazard Analysis and Critical Control Points (HACCP)	HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety. It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.	Detect Critical control Points and manage risks associated with physical, chemical and biological hazards not only in the manufacturing process but also in other life cycle phases of drug development.
5.	Hazard Operability Analysis (HAZOP)	Hazard Operability Analysis (HAZOP) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using guide-words such as "No, More, Other Than, Part of..." are used to indicate potential deviations of relevant parameters from their normal use or design intentions.	Applied primarily in evaluating Process safety hazards and manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and finished products in pharmaceutical industries.
6.	Preliminary Hazard Analysis (PHA)	PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations, and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system.	Applicable for analyzing pre-existing general product type systems, where circumstances prevent a more extensive technique from being used. Even act as precursors to future and modern studies.
7.	Risk Ranking and Filtering	Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk.	Applicable in both quantitative - qualitative assessment of risks and where the portfolio of risks, their underlying consequences to be managed are diverse and difficult to compare using 1 tool and allows filtering and ranking of risks.

for non-critical and unclassified process parameters. Normal operating region is the specific area target operating conditions that typically contain operational variability where the operation of commercial process is carried out. Major challenge in design space development is establishment of effective CPPs from a large pool of unclassified process parameters. Operating parameter based design space construction involves selection and evaluation of all available unclassified process parameters using design of experiments thus reducing the flexibility in final scale up. Hence, appropriate screening designs should be employed to reduce unclassified process parameters and rule out the interactions between them. In case of multiple interrelated CQAs, appropriate design space with acceptable boundaries can be developed by overlaying the response surfaces of CQAs over one another. Design space along with control strategy ensures that the manufacturing process produces product that meets QTPP and CQAs. Figure 18 demonstrates different types of design space.

Design space may be constructed for single or multiple unit operations or for entire process in the presence of multidimensional interactions between CPPs. In case of design space development for single unit operation, overall manufacturing process should be kept in mind along with potential linkages to CQAs and appropriate upstream and downstream steps that could interact with the unit operation. Development of individual design spaces for each unit operation in manufacturing process is an easy task, but a single

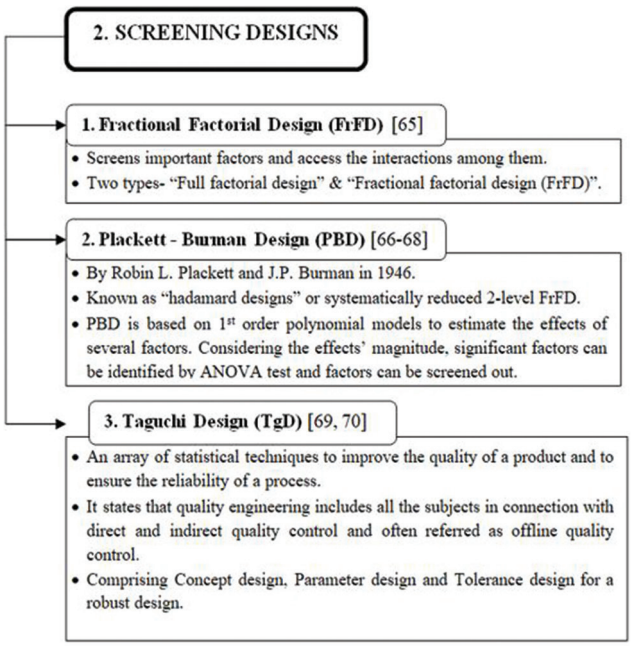

Figure 16: Brief description of different types of screening designs

design space covering all unit operations over a manufacturing process ensures operational flexibility.

Verification of Design Space

Design space verification mainly demonstrates that within design space boundaries, scale up effects are under control and do not adversely affect the expected product quality. There is no need for verification of entire design space during submission by repeating experiments conducted over pilot or lab scale. One or more areas of the design space are verified at initial stages of submission and later the verification is continued over the product lifecycle. Design space verification is guided by the information obtained from risk management studies on potential effects of scale dependent changes over product quality. Design space verification should not be confused with process validation study. Process validation demonstrates the consistency of study at normal operating ranges whereas design space demonstrates the effects of scale changes in new area of design space under control.

Documentation of Design Space

Design space can be suitably presented in the form of ranges of material inputs or process parameters, graphical representations, or more complex mathematical relationships. Information that has to be summarized in common technical document (CTD) should include:

1. All data including conclusions from QRM, experimental designs and models for study, design assumptions, and data analysis.
2. Relationship between proposed design space and other unit operations or process steps.
3. Justification that the control strategy employed keeps the manufacturing process under predetermined boundaries of design space.

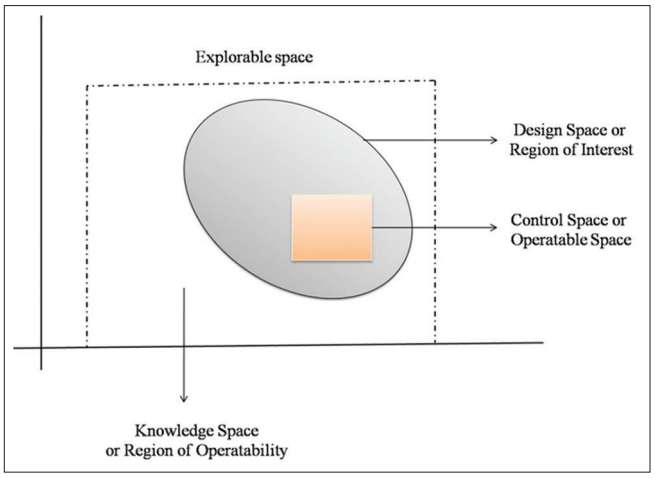

Figure 17: An overview over design space

4. Results and conclusions of study across different scales of production.

Concept of Edge of Failure

Edge of failure may be defined as the established boundaries of material attributes and process parameters beyond which CQAs cannot be met. Establishing edge of failure or failure modes is not an essential part of defining a design space.

Control Strategy

Control strategy is defined as "a planned set of controls, derived from current product, and process understanding that assures process performance and product quality." Control strategies assure that the process will be in control with normal variation in material attributes and process parameters. Control strategy includes input material controls, in process controls or real-time release testing, lot release testing, process monitoring and control, characterization testing, comparability testing, stability testing, procedural controls, design spaces for individual or multiple unit operations, and final product specifications. It provides complete description of how these parameters influence overall product quality, for example, Entacapone, a BCS Class IV drug with cyclodextrin (CD) carrier system has three process parameters, namely, β-CD: Drug ratio, % w/w of crospovidone and PEG 4000 with various operating levels[72] and in the same way the effect of various concentrations of β-CD and hydroxypropyl-β-CD on Modafinil Solubility and thermodynamic parameters of the solubility process was studied and altered using pre-quality design technique.[73]

Comprehensive pharmaceutical development approach should be employed for product and process understanding for proper identification of potential sources of variability. It should ensure that product of required quality will be produced consistently. These controls assigned should be based on product, formulation, and process understanding involving apposite control over CPPs and material attributes. Product and process understanding along with ample risk assessment tools can be used to balance variability for consistent quality in output.

A well-developed control strategy mainly focuses over reduction of risk but does not change the criticality of the

attributes. It ensures that the process meets CQAs and proper realization of QTPP. Control strategy is generally developed and implemented during clinical trials and refined for commercial scale as additional knowledge is gained. Control strategy should be improved over product lifecycle by continuous process verification. Knowledge management is important in the development of a control strategy to ensure ongoing effectiveness of control strategy.[74]

Different control strategies can be employed for same drug product at different sites of manufacture involving major differences in equipment, facilities, systems, and technologies employed. Risk associated with scale-up should be considered in control strategy selection and development using effective QRM tools to ensure effectiveness of control strategy across different scales. Generic sponsors utilize control strategy as reliable means of ensuring product quality as they scale up their product from ANDAs to commercial level.

Current system of quality management involves constrained manufacturing processes and rigorous testing over product lifecycle from drug specifications to end product testing. This conservative strategy helps FDA and CMC reviewers to guarantee consistent quality of end product even if manufacturers cannot identify risk based effects of drug substances or excipients or manufacturing process parameters.

Nature of control strategy changes with the classification of process parameters. If process parameters are left unclassified, control strategy should be developed for extensive testing whereas if classified according to criticality it may lead to reduced end product testing. Development studies mainly involved in classification of UPPs to critical or non-critical. Process parameters if left unclassified are subjected to extensive testing to overcome uncertainty. CPPs are constrained at a multi-dimensional design space to fixed acceptable limits allowing multivariate changes. NCPPs are established under normal operating ranges of design space and may extend over or up to proven acceptable ranges with possibility of univariant changes.

LIFECYCLE MANAGEMENT AND CONTINUAL IMPROVEMENT

ICH Q10 quality guideline provides information over lifecycle management with a well described model for effective quality management for pharmaceutical industry, referred to as "pharmaceutical quality system" that can be implemented at any stage of product lifecycle. This model of pharmaceutical quality system mainly depends on principles of ICH Q8 (pharmaceutical development), ICH Q9 (QRM), international standards organization (ISO) quality concepts, and good manufacturing practices (GMP) regulations. ICH Q10 states that implementation of Q10 throughout product lifecycle should facilitate innovation and continual improvement and strengthen link between pharmaceutical development and manufacturing activities.

Goals of Lifecycle Management

Various stages of product lifecycle with goals and technical activities for quality management include the following:

1. Pharmaceutical development: It aims to design a quality product and its manufacturing process to consistently deliver intended performance of the product. Knowledge from exploratory and clinical studies can be used as the basic inputs for pharmaceutical development.[75]
2. Technology transfer: It includes the transfer of product and process knowledge between developmental stages to large scale manufacturing stage to achieve product realization. It serves as the basis for product manufacturing process, control strategy, process validation, and continual improvement. Technical activities in technology transfer include – new product transfers during development through manufacturing, transfers within or between manufacturing and testing sites for marketed products.
3. Commercial manufacturing: Product realization, efficient control strategy, and continual improvement over product lifecycle are the goals of manufacturing activities. An efficient pharmaceutical quality system should ensure that the knowledge is continually expanded with continual improvement for desired product quality and performance. Technical activities during commercial manufacture include acquisition and control of materials, provision of facilities, utilities, and equipment, production (including packaging and labeling), QA and QC.
4. Product discontinuation: The major aim of product discontinuation is to manage terminal stage of product lifecycle effectively. It involves activities such as retention of documentation, sample retention, continual product assessment, and reporting.

POTENTIAL CHALLENGES OF QBD APPROACH[76]

The understanding and practice of QbD are evolving and gaining momentum in throughout industries and despite the fact of strong business among them, the companies are at different levels of maturity which creates a possibility of facing several challenges in QbD adoption. They are as follows:

1. Internal misalignment (i.e., disconnect between cross functional areas, e.g., R&D and manufacturing sections in industry).
2. Lack of technology to execute (i.e., difficulty in managing data, limited understanding in the way of implication of CQAs).
3. Lack of tangible guidance (i.e., presence of great no. of variables in a formulation may create complexity in understanding and requires a QbD expert).

Numerous key challenges other than mentioned above are demonstrated in Figure 19 with their ways of management and Figure 20 spots multiple myths and facts regarding QbD.

COMPUTER SOFTWARE PACKAGES FOR APPLICATION OF QBD

Besides approval of regulatory authorities for implementation of QbD in pharmaceutical development, various computer software packages are available for user friendly and flexible application of QbD for determining and establishing superior formulation and attaining a final product with pre-estimated

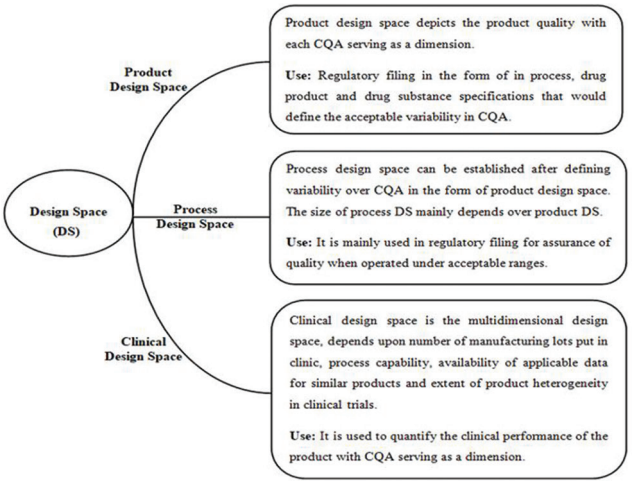

Figure 18: Different types of design spaces

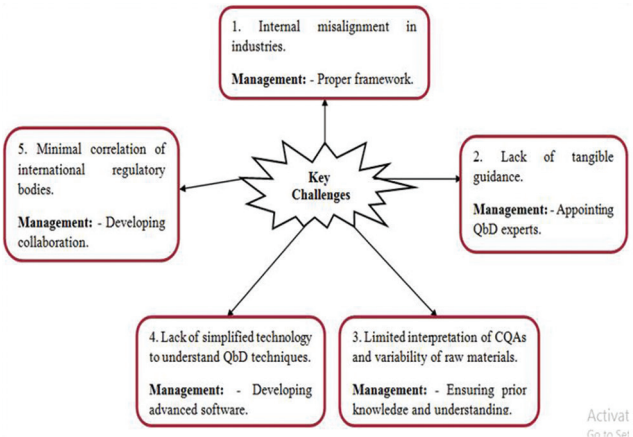

Figure 19: Key challenges in QbD adoption and their ways of management

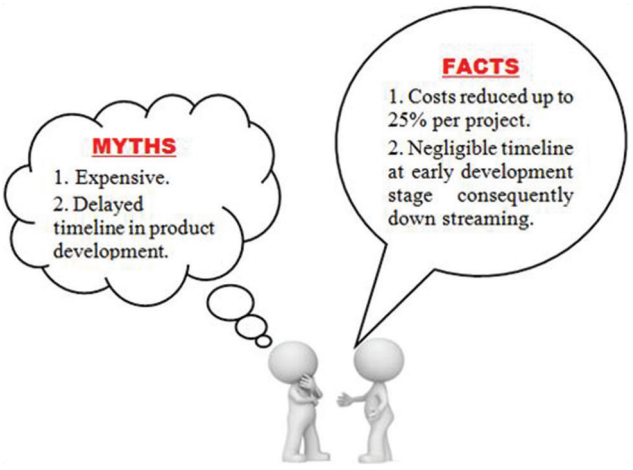

Figure 20: Correlation of myths and facts in view of QbD

quality and efficiency that can be widely used in research and optimization of pharmaceutical formulations.[77] Table 4 shows various marketed QbD software packages and their accessible sources.[57]

Table 4: Various marketed QbD software packages and their accessible sources

S. No	Software	Accessing LINKS
1.	Design-Expert®	www.statease.com
2.	Fusion QbD®	www.smatrix.com
3.	MODDE	www.umetrics.com
4.	Minitab®	www.minitab.com
5.	JMP	www.jmp.com
6.	STATISTICA	http://www.statsoft.com/
7.	THE UNSCRAMBLER	www.camo.com/rt/Products/Unscrambler/unscrambler.html
8.	CODESSA PRO™	www.compudrug.com
9.	DOE KISS and DOE PRO XL	www.sigmazone.com
10.	MATREX	www.rsd-associates.com/matrex.htm

CONCLUSIONS

A drug product development is a "dynamic process" as it unveils multiple challenges time and again. The principle of QbD helps researchers in streamlining and establishing barrier-free ideas with the existing knowledge. Gathering sufficient knowledge with thorough investigation on drug product can help researchers in establishing relevant "SMART" objectives and by following all key elements of QbD in step-by-step manner will ensure in reducing time and improving quality of drug product in drug development cycle. In the due course, one may face potential challenges and with customized approach, they can be confronted as well as managed efficiently thus, making it a standard practice that eventually meets and satisfies the demands of providing low cost – superior quality medications in long run. Implementation of QbD paradigms assures the patient fraternity and regulatory agencies that quality is "built-in" into the product rather than proving it by end-product testing which makes QbD as an omnipresent tool in drug development lifecycle.

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