WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 3, 329-345. Review Article ISSN 2277– 7105

# BRIEF REVIEW ON QUALITY BY DESIGN

**Miss. Mohini S. Jogdande* and Dr. Sachin A. Nitave**

Dr. J.J. Magdum Trust's, Anil Alias Pintu Magdum Memorial Pharmacy College, Dharangutti. Dist: Kolhapur, Maharashtra, India.

Article Received on
21 Dec. 2020,

Revised on 11 Jan. 2021,
Accepted on 01 Feb. 2021

DOI: https://doi.org/10.17605/OSF.IO/6RW8G

***Corresponding Author**
**Miss. Mohini S. Jogdande**
Dr. J.J. Magdum Trust's, Anil Alias Pintu Magdum Memorial Pharmacy College, Dharangutti. Dist: Kolhapur, Maharashtra, India.

## ABSTRACT

Regulatory authorities consider that incremental and unsystematic improvement in unit operations, in isolation, would only have little effect on overall process performance or quality. To assure the quality of the product, a more holistic approach provided by QbD should be adopted. 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". Furthermore, for technology transfer, QbD generated process understanding can make the transition more efficient ICH Q9 together with ICH Q8 and Q10 is one of the ICH Q-topics that encourage further development science based and risk based approaches to quality. The intention of ICH Q9 is to focus the behaviors of industry and regulatory authorities on the two primaries.

**KEYWORDS:** Quality, QbD, ICH, Emphasizes.

## INTRODUCTION

### Quality by Design (QbD)

Regulatory authorities consider that incremental and unsystematic improvement in unit operations, in isolation, would only have little effect on overall process performance or quality. To assure the quality of the product, a more holistic approach provided by QbD should be adopted.[1] 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". In manufacturing of new or marketed products, QbD can help in pre-determining the risk potential of various operations, assuring that suitable control strategies can be applied on

time. Since Qbd is a science-based approach, it provides a basis for optimizing and improving the manufacturing operation without facing additional regulatory filings or scrutiny.[1,2]

**Principles of Quality Risk Management, which are**

The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and the level of effort, formality and documentation of the Quality Risk Management process should be commensurate with the level of risk. To support the implementation of Quality Risk Management into daily operations for Regulators and Industry some members of the ICH Q9 Expert Working Group have prepared a set of slides, which are intended to be used for information purposes in industry, regulators and other facilitators such as consultants.[1,2]

## HISTORY

In past few decades, pharmaceutical companies had spend an enormous amount of resources in their unflagging efforts to assure quality, achieve regulatory compliance, and produce drugs as cost-effectively as possible. Consequently, they employ advance processes and technologies that entail a great deal of scientific sophistication and operational complexity. However, such effort lacks comprehensive, rationale based understanding of these complex processes, associated critical variables and strategies to control these variables, which is pivotal in assuring quality of the product. Little emphasis is paid to identify the root cause of manufacturing failures. Furthermore, no rationale-based approach is followed to predict the effects of scale-up on the final product. This has led to a gap between product quality attributes and their clinical performances, forcing regulatory authorities to set stringent specifications and guidelines for approval of drug products.[1,2,3]

In order to overcome these roadblocks, in 2002, US Food and Drug Administration (FDA) had announced a new initiative- Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, intended to modernize the FDAs regulation in regards to pharmaceutical manufacturing and product quality. The initiative challenged industry to look beyond quality by testing (QbT) for ensuring product quality and performance. Additionally, International Conference on Harmonization (ICH) Q8 guideline was published in May 2006 for pharmaceutical product development, and has been complemented by the ICH Q9 on Quality Risk Management and ICH Q10 for a Pharmaceutical Quality System. These guidelines emphasize quality by design (QbD), a science-based approach for designing formulations and manufacturing processes in order to ensure predefined product quality

objectives. The fundamental assumption underlying QbD is that the quality of the product can be assured only if critical sources of variability is understood and is suitably mitigated or controlled within a defined design space.[1,2,3]

## 1. COMPONENTS OF QBD

### 1.1. Quality target product profile (QTPP)

FDA defines QTPP as the quality attributes related to safety and efficacy of the product. It may include route of administration, dosage form, delivery systems, dosage strength(s), container closure critical to the dissolution of a solid oral product, then the QTPP should include dissolution but not particle size. For an NDA, the QTPP is under development while for the ANDA product, the QTPP is well established based on the properties of the drug substance (DS), characterization of the reference listed drug (RLD) products, RLD label and intended patient population. A typical example of QTPP for immediate release dosage form for generic product development is described.[2,4]

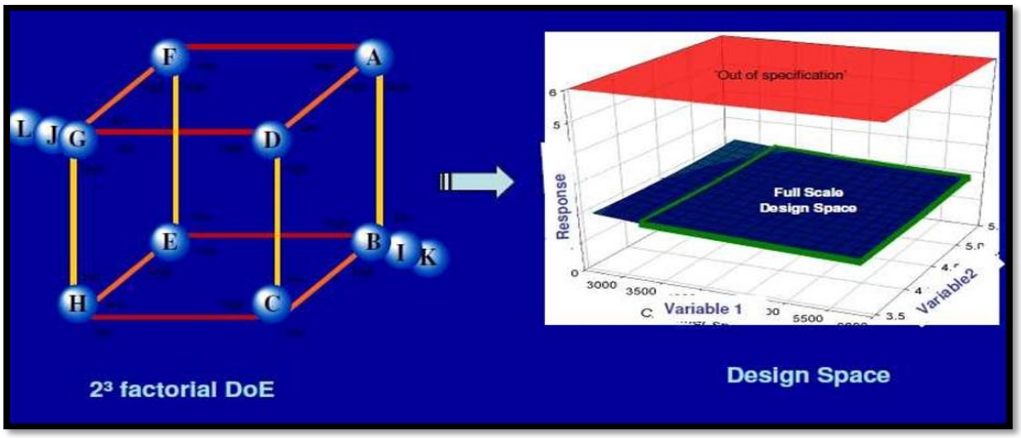



**Figure No. 1: Design of experiment (DOE).**

### 1.2. Critical quality attributes (CQA)

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 that should be within an appropriate limit, range, or distribution to ensure the desired product quality". This indicates that CQAs are subsets of QTPP that has a potential to be altered by the change in formulation or process variables. For example, QTPP may include additional quality attributes of the drug product such as strength and dosage form, which are not the part of CQA as it will not change during drug development process. However, QTTP attributes such as assay, content uniformity, dissolution, and permeation flux will also be a part of CQA

as they may be altered by formulation or process variables. List of potential CQAs for immediate release dosage form for generic product development is described.[3,4]

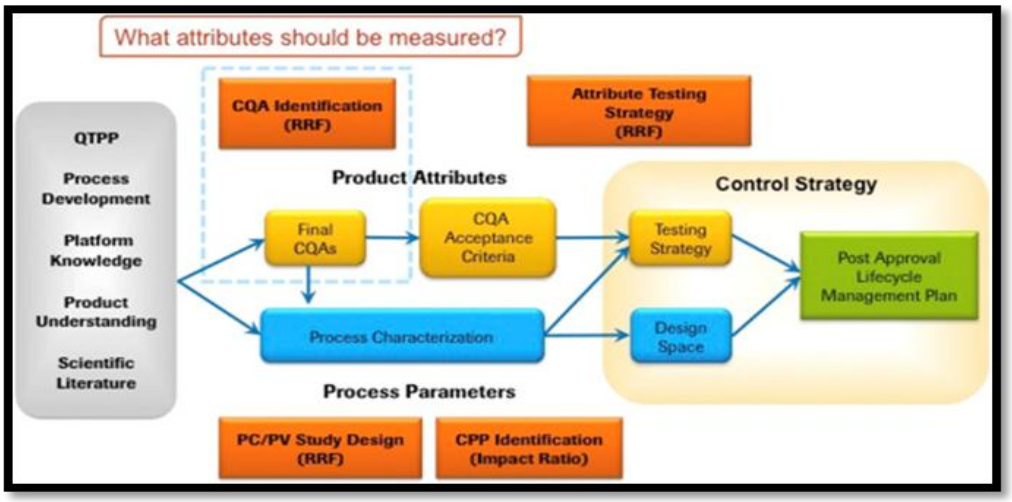



**Figure No.2. Critical quality attributes (CQA).**

### 1.3 Quality risk management (QRM)

FDA defines QRM as a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. The goal of QRM is therefore to identify risks within a process or event, analyzing the significance of these risks, and takes appropriate measures to mitigate such risks if deemed unacceptable or equipment.[4]

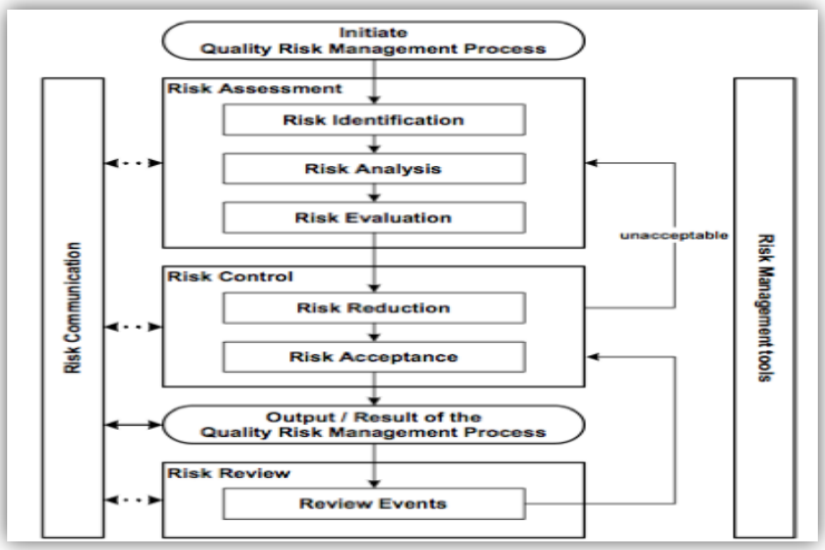
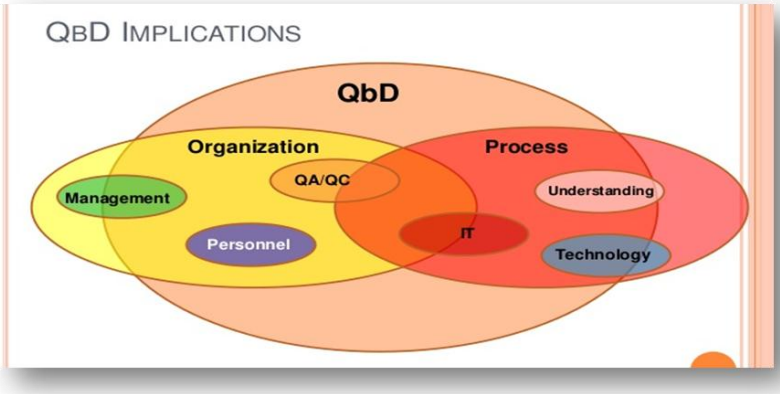



**Figure No. 3: Overview of typical quality risk assessment process.**

## 2. KEY ASPECTS OF QBD INCLUDE




### 2.1. The Target Product Quality Profile (TPQP)

TPQP has been defined as a "prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, ofa drug product is realized".[6]

TPQP forms the basis for product design in the following way.

- Dosage form
- Route of administration
- Strength, maximum and minimum
- Release/delivery of the drug
- Pharmacological characteristic
- Drug product quality criteria

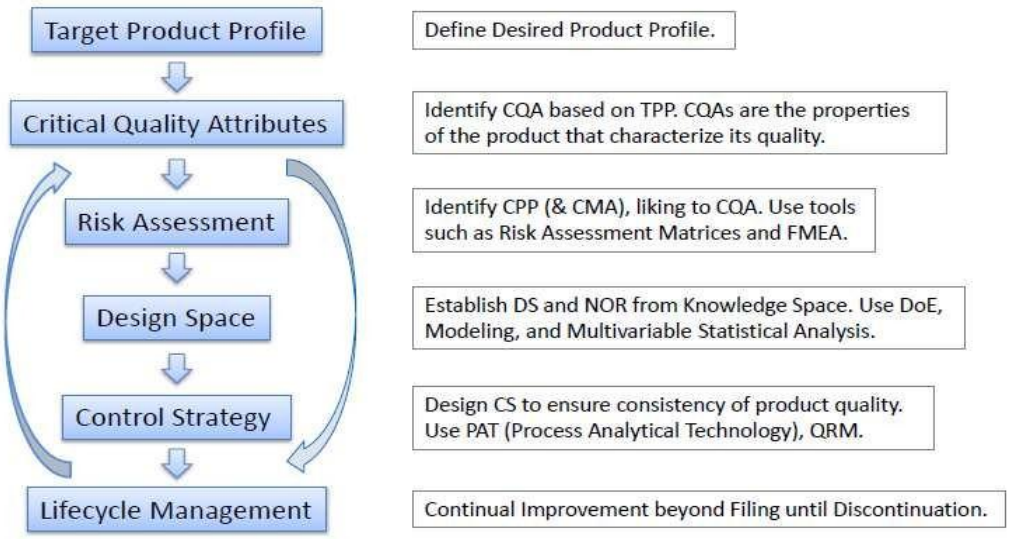



**Figure No. 4: Elements of Pharmaceutical Development.**

### 2.2. Critical Quality Attribute

Once TPQP has been identified, the next step is to identify the relevant CQAs. A CQA has been defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within inappropriate limit, range, or distributed to ensure the desired product quality" Identification of CQAs is done through risk assessment as per the ICH guidance Q9. 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 CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability.[6]

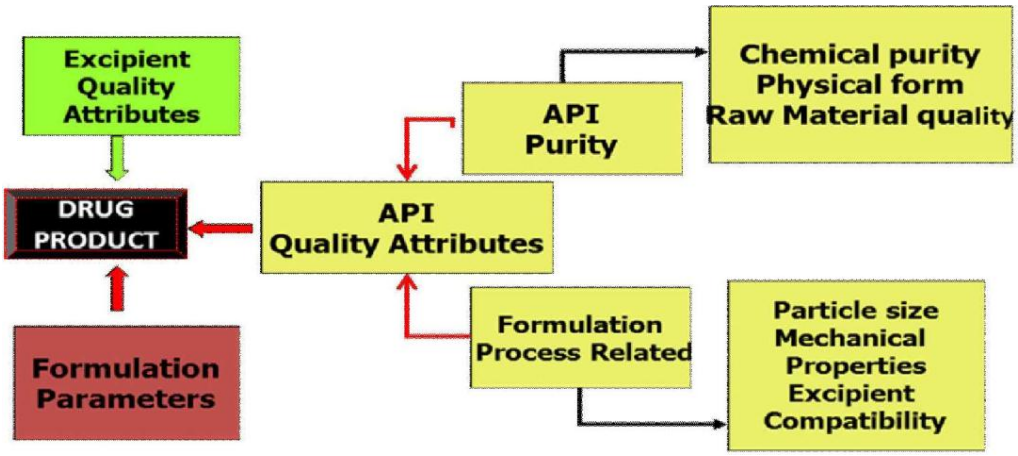



**Figure No.5: Role of (CQA).**

### 2.3. Critical Process Parameter

Critical process parameters (CPPs) are defined as "parameters whose variability have an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality "Process robustness is defined as the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time. Process capability is a statistical measure of the inherent process variability for a given characteristics. The most widely accepted formula for process capability is six sigma. Process capability index is the value of the tolerance specified for a particular characteristic divided by the process capability, which is defined as follows: Process capability index (CpK) = Upper limit of specification - Lower limit of specification6 standard deviation If the CpK is significantly greater than one, the process is defined capable. If the process capability is low, there are five step procedures to progressively reduce the variability of the process.[6,7]

**These five steps are**

1. Define
2. Analyze
3. Improve
4. Control

**Classification of process parameters**

**Table No.1: Critical Process Parameter.**

| Parameter Type | Definition | Sensitivity |
|---|---|---|
| Non-CPP | Non critical | • No failure in target product quality profile observed in the potential operating space. |
| UPP | Critically Unknown | • Not established<br>• The default in the absence of pharmaceutical development. |
| CPP | Critical (control needed to ensure quality | • Interaction with other parameters in the proven acceptable range (PAR) |

### 2.4. Risk Assessment

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. The initial list of potential parameters which can affect CQAs can be quite extensive but can be reduced and prioritized by quality risk assessment (QRA).[6,7]

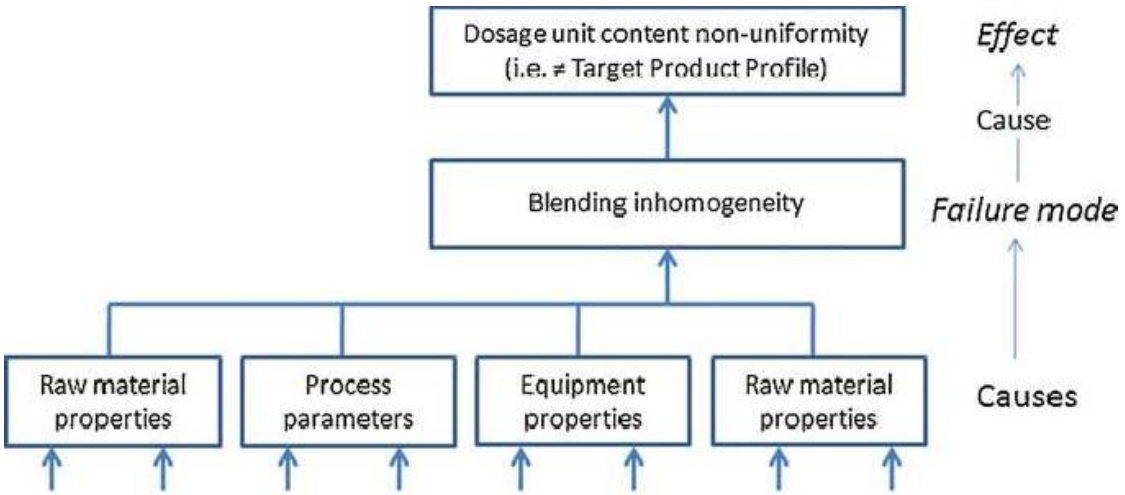



**Figure No. 6: Risk identification: fault tree analysis of variable content uniformity.**

### 2.5. Design Space

The ICHQ8 (R2) States that the design space is multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Design space is potentially scale and equipment dependent, the design space determined on the laboratory scale may not be relevant to the process at the commercial scale. Therefore, design-space verification at the commercial scale becomes essential unless it is confirmed that the design space is scale-independent.[7]

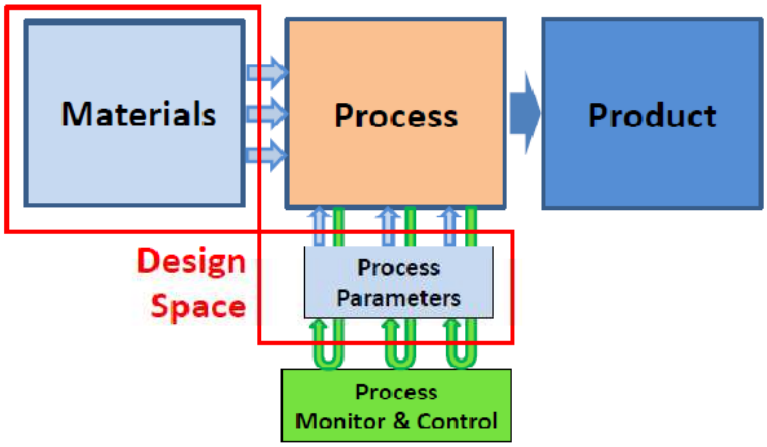



**Figure No. 7: Design space.**

### 2.6. Control Strategy

The ability to evaluate and ensure the quality of in-process and/or final product based on process data which typically include a valid combination of measured material attributes and process controls. Control strategy is defined as "a planned set of controls, derived from current product and process understanding that assures process performance and product quality". The control strategy in the QbD paradigm is established via risk assessment that takes into account the criticality of the CQA and process capability. Particularly, the control strategy may include:[7,8]

- 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.

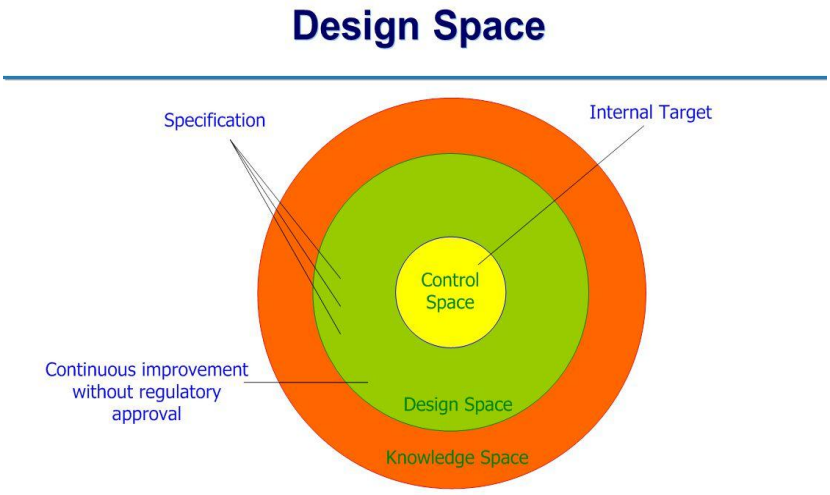



**Figure No. 8: Design space.**

### 2.7. Life Cycle Management

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 to 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 (excursions) on product quality.[7,8]

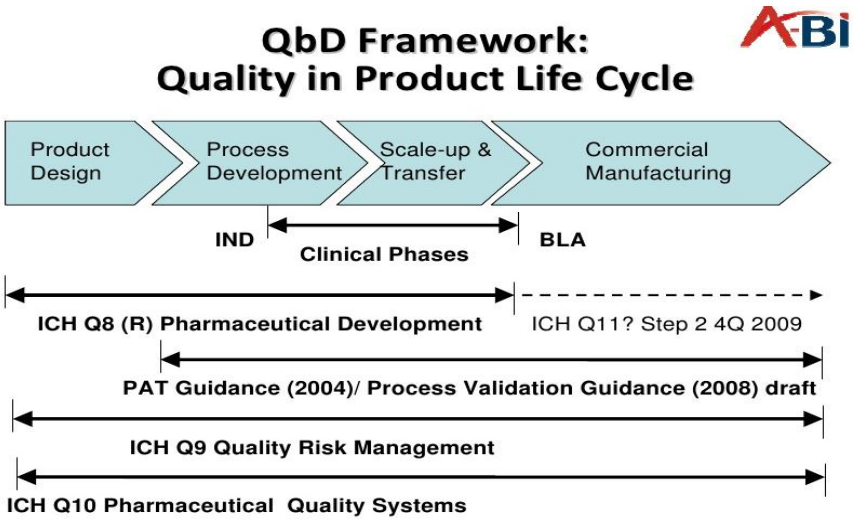



**Figure No. 09 Life Cycle Management.**

## 3. TOOLS OF QUALITY BY DESIGN

### 3.1. Design of Experiments (DOE)

Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. It has been suggested that DOE can offer returns that are four to eight times greater than the cost of running the experiments in a fraction of the time. Application of DOE in QbD helps in gaining maximum information from a minimum number of experiments. When DOE is applied to a pharmaceutical process, 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.[7,8,9]

### 3.2.Process Analytical Technology (PAT)

PAT has been defined as "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". The goal 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."[9]

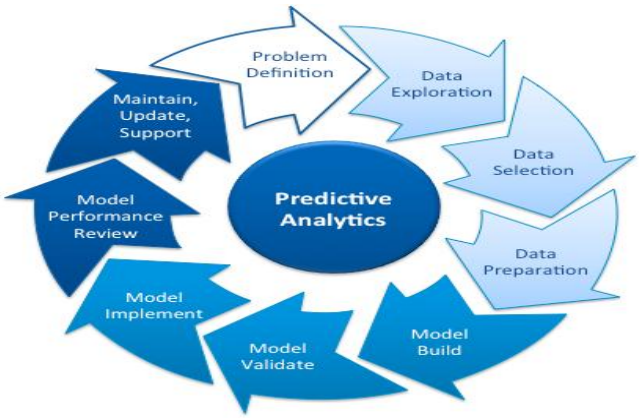



**Figure No. 10: Process Analytical Technology (PAT).**

### 3.3. Risk Management Methodology

Quality Risk Management is defined 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". 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. 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)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering[10,11]

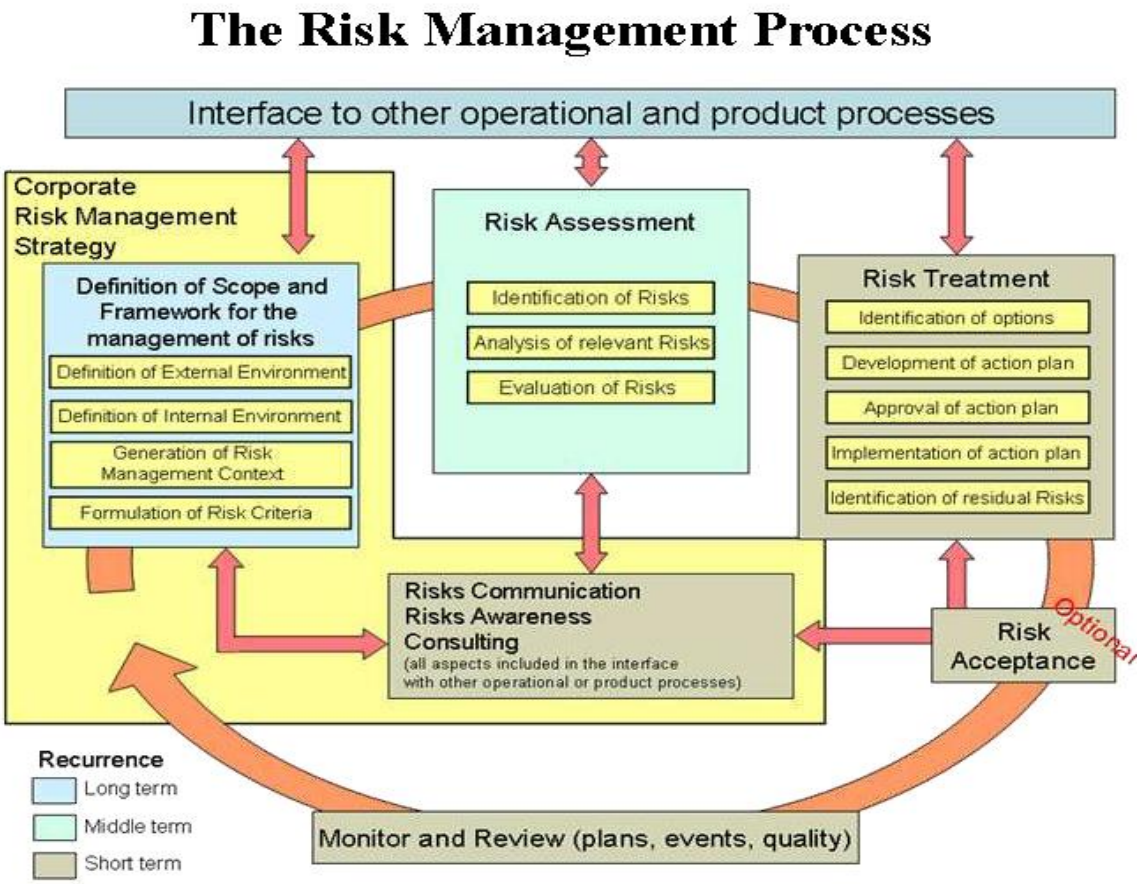



**Figure No.11 Risk Management Methodology.**

## 4. Aspects of application of QbD to analytical method

Various aspects explained in pharmaceutical development are also put into practice for development of analytical method in QbD paradigm. Some key aspects are discussed hereunder.[10,11]

### 4.1 Analytical target profile (ATP)

"QbD is a systematic approach to product and process design and development," Hence it begins with determination of goal or method intent. In this emphasis is given on the product and process understanding. ATP is way for method development or it is simply a tool for method development. It describes the method requirements which are expected to be measured. In general the goal of the chromatographic method is separation, quantification and identification of drug substance, impurity or degradedness. Impurity is considered to be the critical quality attribute (CQA). It provides framework to method development which helps for further planning. It decides what to be measured and within what limit it is required to be measured. ATP is in complete accordance with ICH guideline.

### 4.2. Method design

Method design is prepared for appropriate availability of material and setting various experimental conditions. In this the reagents required are made available. Regional and geographical conditions are taken into consideration. Feasibility of instruments is checked and experimental design is prepared. In this use of various flowcharts decision tree can be made for correct implementation. In case of HPLC method development scouting is done. In this large number of experimental conditions were tried ($p^H$, temperature, columns, and buffers). Data are collected and software is generated by entering obtained results in terms of values from actual experiments. Then that data base is generated which helps to predict the effect of various chromatographic conditions in large number. This type of software helps to predict outcome without actual experimentation. Among various methods; suitable method to serve the desired purpose is chosen. For example, to determine impurities, HPLC with detector like PDA can be used. In method design, method that meets method requirement is established. Method design may be repeated or modified as and when required throughout the life cycle. Method development strategy (MDS) includes design of experiments (DoE). It is helpful in risk assessment by gaining knowledge about existing method and allows for effective control strategies for critical parameter.[10,11]

### 4.3. Critical quality attributes (CQA)

Factors which directly affect the quality & safety of the product are first sorted out, and its possible effect on method development is studied. Understanding of the product and method will help to sort the CQA. If drug product contains the impurity which may have direct effect on quality and safety of drug product it is being considered the critical quality attribute for the HPLC method development of that particular drug compound.[10,11]

### 4.4. Risk assessment

It is link between input process variable and CQA. Various tools for risk assessment are,

1. Ishikawa or fishbone diagram,
2. Failure mode effect analysis (FMEA),
3. Pareto analysis.

Once the risk is assessed it is grouped into three categories.

1. High-risk factors that should be stringently controlled, typical high-risk factors that can be fixed at the time of method development that includes data analysis methods and sample preparation methods.
2. Potential noise factors,
3. Factors that can be explored experimentally to determine acceptable ranges.[10,11]

### 4.5. Method qualification

Once the method is designed keeping analytical target profile (ATP) in mind with taking care of the risk involved in development, the next step comes is method qualification this is to ensure that method is being performed as intended. It involves equipment qualification which is part of method qualification. It is divided in, method installation qualification (MIQ), method operational qualification (MPQ), and method performance qualification (MPQ).[11]

**Design Qualification**

1. Installation Qualification
2. Operational Qualification
3. Performance Qualification

**Combined Parameters for Operational Qualification and Performance Qualification.**

**Table No.2: Combined parameters for operational qualification and performance qualification.**

| Module | Parameter |
|---|---|
| Injector | Precision of injection volume |
| | Linearity of injection volume |
| | Injection carryover |
| | |
| Autosampler | Thermostatting precision |
| Solvent delivery system | Flow rate accuracy |
| | Mobile phase proportioning |
| | Flow rate precision |
| | |
| Detector | Wavelength accuracy |
| | Noise |
| | Drift |
| | Linearity of detector response |
| | |
| Column oven | Thermostat ting precision of column oven |

### 4.6. Control strategy

It is important that set method performs as intended and consistently gives accurate results, for that purpose control on method is required. A factor identified to have risk has to be controlled. More attention is given to the high risk factors. System suitability can be checked and verified time to time by having control over it. On ground of practical example; the risk assessment can also help identify a specific control strategy. For example, during robustness studies for an Atomoxetine hydrochloride HPLC impurity profile method, it was found that resolution of the impurities of interest followed the same trend when method parameters such as *n*-propanol and temperature were varied. As a result, an early eluting impurity pair was chosen for system suitability and became a convenient method control strategy because the two compounds involved were easily obtained. Validation remains the formality it is done in similar way to that of traditional method development in validation (ICHQ2) but in traditional approach method validated after development i.e. it is like checkbox tool, and in QbD the validation parameter in ICHQ2 are consider as method intent.[11,12]

### 4.7. Life cycle approach

Life cycle approach differs from that of the traditional approach of method development. According to Moorefield it includes continuous improvement of method performance and the design space allow flexibility for Continuous improvement in analytical method can be done without prior regulatory approval because of design space made previously. Knowledge

gained from risk assessment and data collected from design of experiments can be used as the repository of knowledge to make justified changes wherever required. A complete process analytical method development in QbD environment is summarized in the following flow chart.[11,12]

## 5. QbT and QbD[11,12,13]

**Difference between QbT and QbD**

**Table No. 3: Difference between QbT and QbD.**

| Elements | QbT approach | QbD approach |
|---|---|---|
| Product process development | • Data intensive submission disjointed information without big picture.<br>• A specification based on batch history.<br>• Frozen process‟-discouraging changes.<br>• Focus on reproducibility-often avoiding or ignoring variation.<br>• Focus on reproducibility-often avoiding or ignoring variation. | • Knowledge rich submission- showing product knowledge and process.<br>• A specification based on product performance requirement understanding.<br>• Flexible process within the design space allowing continuous improvement. |
| Risk management | • Compliance focus changes require prior approval.<br>• Control strategy managed mainly by intermediate & end product testing.<br>• Quality decision divorced from science & risk evaluation. | • Regulatory scrutiny adjusted to the level of process understanding continuous improvement allowed within the design space.<br>• Risk based; control shifted up strong real-time release<br>• A decision based on process understanding & risk management. |
| Validation | • Fixed; validation on 3 initial full-scale batches, focus on reproducibility. | • Adjustable within the design space continuous verification within a design space; focus on control strategy |

| | | |
|---|---|---|
| | | & robustness |
| Process control | • In-process testing for go/no-go offline analysis; slow response.<br>• Quality assured by testing & inspection. | • Management of variability process control focused on critical attributes, continuous quality verification.<br>• Quality built into product & process by design, based on scientific understandings. |
| Lifecycle management | • Reacting to problems and OOS; post approval changes needed. | • Continual improvement enabled within the design space. |

## CONCLUSION

The goal of a well-characterized method development effort is to develop a reliable method that can be demonstrated with a high degree of assurance to consistently produce data meeting predefined criteria when operated within defined boundaries. QbD can be applied to the development and evaluation of analytical methods. During method development, all potential factors (the inputs) and all critical analytical responses (the outputs) are studied to determine the relationships. Critical analytical factors are identified in an approach that parallels what is described for process development in ICH Q8 and Q9. The QbD process on an active partnership of analytical scientists at both the development and operational laboratories as methods are developed and as factors that lead to potential method failures are identified and controlled. Such a repository (in line with concepts described in the draft ICH Q10 will enable continuous improvement and change control of the method to take place throughout its lifecycle.

A QbD approach for analytical methods that includes risk assessment, robustness testing, and ruggedness testing is much more rigorous than ICH validation requirements (Q2(R1)). It also includes an assessment of method variability compared with the specification limits, which is one of the most important method attributes to test when deciding whether the method is fit for its purpose.

## REFERENCES

1. Rathore AS, Winkle H. Quality by design for biopharmaceuticals. Nat Biotechnol, 2009; 27(1): 26-34.
2. Adam S, Suzzi D, Radeke C, Khinast JG. An integrated Quality by Design (QbD) approach towards design space definition of a blending unit operation by Discrete Element Method (DEM) simulation. Eur J Pharm Sci., 2011; 42(1-2): 106-15.

3. Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm Res., 2008; 25(4): 781-91.
4. US Food and Drug Administration. Guidance for industry: Q8(R2) pharmaceutical development. US Department of Health and Human Service (FDA, Rockville, MD, 2009.
5. Looby M, Ibarra N, Pierce JJ, Buckley K, O'Donovan.
6. ICH Q8 (R2), Pharmaceutical Development, Part I: Pharmaceutical Development, 2009.
7. ICH Q9, Quality Risk Management, 2005.
8. ICH Q10, Pharmaceutical Quality Systems, 2008.
9. US Food and Drug Administration (FDA), Department of Health and Human Services, Pharmaceutical Quality for the 21st Century A Risk-Based Approach Progress Report, 2007.
10. US Food and Drug Administration (FDA), Guidance for industry PAT-A framework for innovative pharmaceutical manufacturing and quality assurance, FDA, Washington, DC, USA, (2004)Lawrence, X. Raw, A.Lionberger, R. Rajagopalan, R. Lee, L. etal. U.S. FDA question-based reviewfor generic drugs: A new pharmaceutical quality assessment system, *J. Generic Med.*, 2007; 4: 239–248.
11. Rathore, A.S. Winkle, H. Quality by design for biopharmaceuticals, *Nat Biotechnol*., 2009; 27: 27-34.
12. Nadpara, N.P. Thumar, R.V. Kalola, V.N. Patel, P.B. Quality By Design (Qbd) : A Complete Review, *Int. J. Pharm. Sci. Rev. Res*., 2012; 17: 20-28.
13. Gawade, A. Chemate, S. Kuchekar, A. Pharmaceutical Quality by Design: A New Approach Product Development. *Res Rev: J Pharm. Pharm Sci*., 2013; 2: 5-12.