



## INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

### APPLICATION OF QUALITY BY DESIGN (QBD) APPROACH TO PHARMACEUTICAL INDUSTRY



IJPRBS-QR CODE

RAVI TIWARI, SUKHADA KULKARNI, AMRITA PANDA



PAPER-QR CODE

Department of Pharmaceutical Chemistry, SVKM's NMIMS, School of Pharmacy and Technology, Shirpur, Maharashtra, India.

#### Abstract

#### Accepted Date:

22/12/2012

#### Publish Date:

27/02/2013

#### Keywords

Quality by Design,  
Design of Experiment,  
Process Analytical  
Technology

Quality by Design has brought with it a newer vision towards development of pharmaceutical industry. In the development process of any pharmaceutical product quality is the most important factor. The main objective of this article is to focus on process parameters which are required to achieve a high accuracy and efficiency with a scientific understanding of design of process. A prospective and dynamic output of quality characters of the drug are achieved by a systematic approach of quality by design.

#### Corresponding Author

Mr. Ravi N. Tiwari

---

## **INTRODUCTION**

The principles of quality by design are widely used by many of the pharmaceutical industries in manufacturing and development. It is a new approach towards the use of more scientific and systematic applications in manufacturing and development. It ensures the enhanced product quality by improved analytical processes. It is described in ICH (*International Conference on Harmonization*) Q8, Q9 and Q10 guidance documents. It mainly focuses on target product quality profile, design of the manufacturing with thorough understanding and to maintain consistency in product's quality. Quality by design replaces the current approach by considering the multidimensional aspects of process involved in production of the drug like quality of raw materials, life cycle of the drug, design space, avoiding variations in products and decreased risk for patients. According to some experts, the quality of drug cannot be tested after formulation but it should be built within. Many pharmaceutical companies had no co-operation between their departments this brought them up to build up a better quality

throughout product's life cycle. After this adaption, FDA initiated two important guidelines in ICH Q8 pharmaceutical development and ICH Q9 quality risk management.

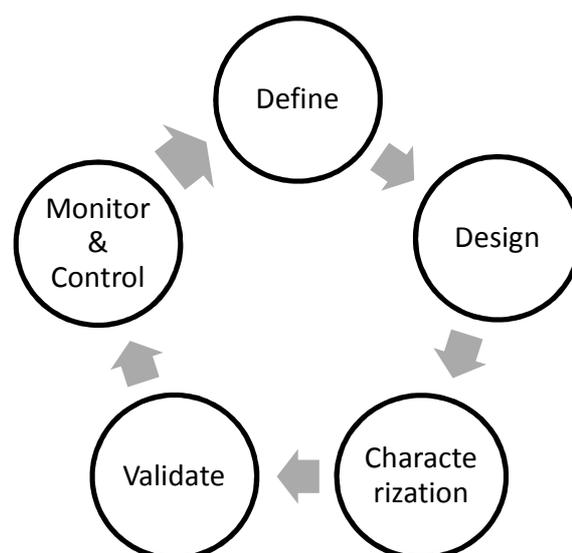
United States Food and Drug Administration (US-FDA) launched an innovating concept of quality by design through 'Pharmaceutical CGMPs for the 21<sup>st</sup> Century: A Risk-Based Approach', in August, 2002 along with Process Analytical Technology (PAT). The concept of QbD explains the in-built quality of the product right from the quality of raw materials, design space, method employed in production, experimental design, etc.

Many of the pharmaceutical companies were suffering from the problem of increasing amount of waste products than the required drug product. Later the problem was found to be with manufacturing inability to predict effects of scale-up on the final product as well as an inability to understand root causes for manufacturing errors. But afterwards the industry started considering the problem at global level because of the increasing demand and variations in the climatic changes of various regions on the globe. For

the development of any new drug, various factors needs to be taken into consideration such as demand, available resources, time required to manufacture, process employed, cost efficacy, etc. Conventional methods for developing a new drug were found to be more time consuming and less cost efficient. Hence the need for adoption of some new concepts for better analytical processes with more efficiency and improved techniques arouse and the concept of quality by design was brought into focus.

Quality by design was preferred as it was cost efficient and provided the high level of accuracy. It found to be more productive and hence widely applied by many of the industries. It assures enhanced product reliability and reproducibility for patients. Industry's vision is always for better and improved skills that will reduce the labour work and constructive results should obtain. Using the concepts of quality by design, analytical methods of validation and transfer of products can be evolved with the improved techniques and more efficient processes. When any new product is in the process of designing and development, company has to define the desired

performance of product and products critical quality attributes. On the basis of this, proper manufacturing method is developed to meet these attributes.



**Figure 1 Pharmaceutical manufacturing process**

Above Figure 1 illustrates different phases in pharmaceutical manufacturing processes: define, design, characterization, validates, monitor and control. In the last link that is, **monitor & control to define**, there is an opportunity to identify the improvement required in the applied process. When changes are applied at this phase, it will again move throughout the process with improvement. Design space is one of the most important considerations during the process of product development. ICH

guidance Q8 defines design space as *'the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality'*<sup>1</sup>.

The concept of Quality by design was first brought into focus by a well known quality expert Joseph N. Juran in various publications.

QbD differs from current approaches in the following ways:

- In current approach quality of drug is approved by testing and inspection, but in QbD approach quality of a drug is built within by proper design space and with scientific understanding.
- In current approach, the submitted data shows disjoint information about product and without its thorough understanding. Whereas in QbD approach, submitted data shows entire knowledge about product with process understanding.
- Current approach focuses on reproducibility whereas Qbd focuses on desired qualities and controls variations in the product.

- In the current approach since the manufacturing process is fixed for starting material, variability in finished product is observed. But in QbD approach, controlled manufacturing process is applied on starting material, consistency of product is achieved.

As given by ATSM there was a huge difference in traditional and QbD based pharmaceutical company because of adaption of new techniques by it. It was recognized that quality is not affected by how much tests are performed during its development but on the formulations, excipients how it is manufactured and packing attributes.

Quality comes into account when time resources are effectively and efficiently utilized. This paper focuses not only on the quality but also the technical aspects utilized in QbD and the most basic requirement is controlling strategy

### **What is Quality by Design?**

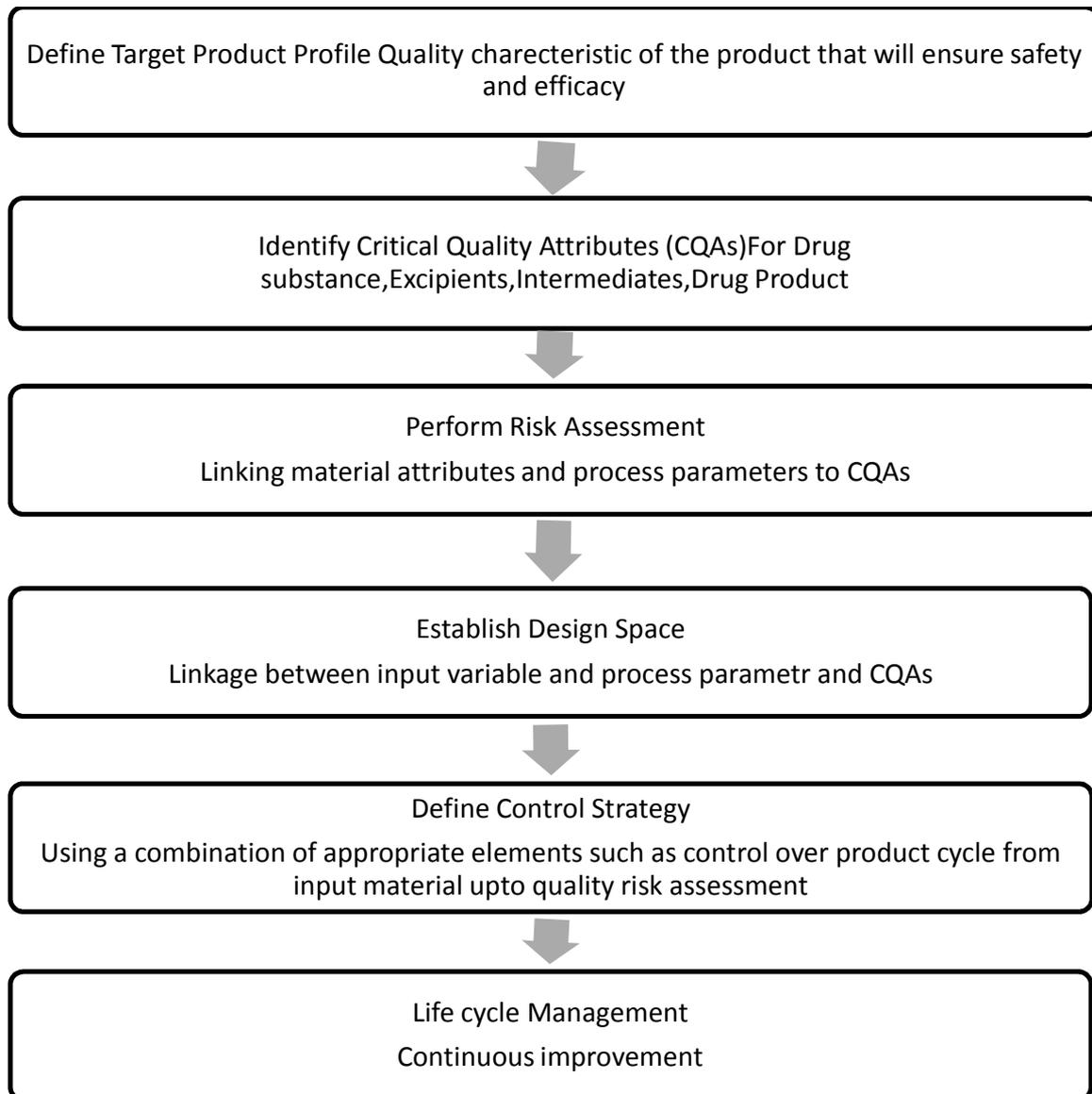
Before defining QbD first we need to understand what quality is. Quality is a product free from contamination and reproducibility that could produce its best effect (as per Woodcock). Further Quality

by design as defined by ICH is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. This definition shows a co- relation between formulation and manufacturing which basically identifies the quality of product which can be critical to patients which is based on Critical Quality Attribute(CQA) and thus develop in it attributes that would help to get a high and better quality product.

QbD is not fixed like traditional manufacturing process but has included a new area of design space and PAT a new innovation which helps to get the feedback at specific and required time. The variability of product is very less and the product developed is efficient, effective and safe for intended use by the patients. The QbD involve a few steps regarding its process-

1. Firstly which drug is to be produced is targeted with the excipients and formulations utilized.
2. Secondly there should be continuous monitoring of the product to be produced to get a better quality product.
3. Third is risk assessment which would arise and should be controlled in primary stage.
4. Fourth is to check out if the inputs and parameters are within the range of utilization as per Design Space
5. A strategy should be made so as to check upon the product quality, manufacturing is not affected.
6. To produce high quality product every time, the measurements and improvement at every step needs to be done<sup>2</sup>.

**Steps of Quality by design**



**Figure 2 Steps of quality by design**

Above figure illustrates the steps involved in the process of implementation of Quality by Design.

QbD components include knowledge space, design space and control strategy.

Knowledge Space: There should be a prior knowledge of the process which will get utilized in the product manufacturing. To develop the quality attributes within the product to be utilized. This is the initial stage where it got to know the facility to be implemented.

Design Space: As defined by ICH-Q8 the established range of process parameters that has been demonstrated to provide assurance of quality.

Control Strategy: A planned set of controls which are needed during the product process and also during raw materials utilization. When it includes CQA and Design Space the product can be obtained without any delay.

#### **The Target Product Quality Profile (TPQP) - *Beginning with the end in mind***

The target product profile is a summary of the drug development program described in the context of prescribing information goals. The Target product quality profile is the natural extension to the concept of TPP. It deals with the quality characteristics of the drug such as safety, efficacy and process of manufacturing that leads to reach desired quality. TPQP is a guide to establish formulation strategy and keep the formulation efforts focused and efficient. Factors that to be considered for desired target product quality profile are as follows –

- Identify critical quality attributes of the drug product

- Route of administration (oral versus Intravenous drug product)
- Type of dosage form (immediate versus modified release)
- High dose versus low dose
- Target population
- Type of therapy (life saving versus quality of life)<sup>3</sup>.

**Table 1**

#### **Target Product Quality Profile (TPQP) V/s Target Product Profile (TPP)**

TPQP	TPP
Dosage form	Description
Appearance	Clinical Pharmacology
Identity	Indicator & Uses
Strength	Contraindications
Assay	Warning
Uniformity	Precautions
Purity/Impurity	Adverse Reactions
Stability	Drug abuse & Dependence
Dissolution/D isintegration	Over Dosage
PK/BE	Dosage & Administration
	Clinical Studies

The target product quality profile not only describes the identification of a product but also facilitates cohesive decision-making and optimal use of a product. TPQP identifies the opportunities that enhance the understanding about multidimensional

qualities of a product. There are specific targets about the product's quality which are considered to be target product quality profile & they are as follows –

**Table 2**  
**Quality targets of a drug product**

Quality Attribute of a Drug Product Target	
Dosage form	Immediate release capsule
Identity	Oval , White
Appearance	Ranitidine
Strength	150 mg
Assay	95 – 105%
Uniformity	Meets USP
Impurities	Impurity 1: NMT 0.5% Impurity 2: NMT 0.2% Others: NMT 0.1% Total: NMT 1.0%
Dissolution	pH 1.2: NTD 85% in 30 min pH 4.5: NLD 85% in 30 min pH 6.8: NLD 85% in 30min
Bioavailability /Bioequivalence	Bioequivalence to RLD

### Design of Experiments

A structured analysis wherein inputs are changed and differences or variations in output are measured to determine the magnitude of the effects of each input. In simple words it basically focuses on how

different designs implemented affect the final product<sup>[4]</sup>. Its main goal is -

1. It reduces the impact of materials given in input
2. It focus on parameters of interaction
3. Checks on experimental errors
4. Obtain maximum output

The methodology adapted for Design of Experiment is

1. Choose the layout that is the design structure
2. Perform any random experiment
3. Analyze the data or output
4. Create multidimensional model

Design Space: Multidimensional combination and interaction of input and process parameter that is estimated for desired quantity. It can be established for any process. Control Space was utilized previously to obtain a quality and patented drug. This Control Space included many units thus was expensive, required a huge space and was also time consuming. To move from control space 1 to control space 2 demanded the approval of regulatory bodies but as design space came into existence there was no requirement of such as all the work could be done in one area<sup>5</sup>.

To utilize a design space prior knowledge as well as manufacturing experience should be there. Design space are added to have a change in formulation and manufacturing process that can provide with genuine data to support through product development and have a check on the ingredients, excipients utilized in it, changes in the formulation and manufacturing process of a product is the basic cause for design space to enter<sup>2</sup>.

Any additional development in studies which would help to enhance over knowledge in product performance over a wider range, if these all are included -

1. Risk could overcome by proper inspection
2. It would increase manufacturing ability
3. Help to obtain quality product in a specific time

Establishment of design space was done as it

1. Established the relation between CQA and CPP
2. Process parameters are determined which would alter the product quality and what are the changes needed

The controlling parameters in a design space:

1. Basic requirements - Particle size, hardness, surface area with ingredients and excipients utilized are proper
2. Operational units - Water content in granules or other blends used
3. Machine parameters - What are machines required the blender or compressor used

Design space can be examined by making work not in lab but as batch equipments. The work of design space starts from product selection to whole lifecycle of the product.

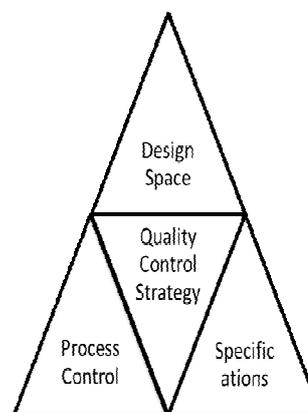
Control Strategy: A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. This ensures that the product every time obtained has a consistent quality which includes in it the materials utilized, processes control and management may it be a single unit or multiple operation. The control strategy has a check upon all process parameters that are to be included within product life cycle as per the requirements of the patients<sup>7,8</sup>.

Control strategy are given as

1. Minimal: In this the intermediate and final product are tested
2. Enhanced: Risk factor is also included to obtain a required and reduced time taken product.

Knowledge of product processing and what could be the scope of variability must be known. This would help to know the final product quality and also minimize the testing process. This both combination may help to know what may be the control procedure adapted so as to reduce the cause of risk and obtain a better quality product. The process understanding can help to built up a new manufacturing process and new adaptive procedure. Control strategy include many elements and depends on end product test and real-time reduce testing. Control strategy can be develop by having a structured and planned process in which all pharmaceuticals department cope up together to provide a better manufacturing process. Control strategy no doubt ensures the quality, quantity, efficiency and safety of product but it also does fulfill the business objective that is team effort, safety of person and

environment and profit. The risk assessment is a major area of control strategy<sup>9</sup>.



**Figure 3 Major areas for control strategy**

### **Critical Quality Attributes**

Critical quality attribute is one of the most important elements of QbD & 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”. In manufacturing of any pharmaceutical product, series of unit operations such as mixing, milling, granulation, drying, compression, coating, etc are involved. According to ICH Q7 guidelines, GMPs (Good Manufacturing Processes) for various operations are different as per product’s requirement & hence conditions required are also different. The process parameters that to

be taken into consideration for deciding CQA are equipment and equipment setting, operation conditions (such as temperature, pH, pressure, time ,etc), environmental conditions like humidity, atmospheric pressure. Process parameters are said to be critical when there is any realistic change that result in failure of the product to meet the desired quality of a product.

There are three important criteria's while considering the CQA for a particular product;

- I. Impact of raw materials i.e. nature of excipients & their physical properties, functional properties are required to be specifically defined.
- II. Properties of the API used in manufacturing such as physical properties, its purity, assay procedure, identity of active ingredient.
- III. Properties of a drug product (API + excipients) such as mechanical & physical properties, assay procedure, rate of

dissolution, odor, description & purity of the drug product.

And moreover safety & manufacturability are the important factors that define the requirement of critical quality attributes for a drug substance.

#### **Critical Material Attribute (CMA)**

A physical, chemical, biological or microbiological property or characteristic of a material that should be within an appropriate limit, range or distribution to ensure desired product quality is known as critical material attribute.

#### **Critical Process Parameters (CPP)**

A process parameter whose variability has an impact of critical quality attribute & therefore should be monitored or controlled to ensure the process produces the desired quality is known as critical process parameters.

CMAs and CPPs: Example

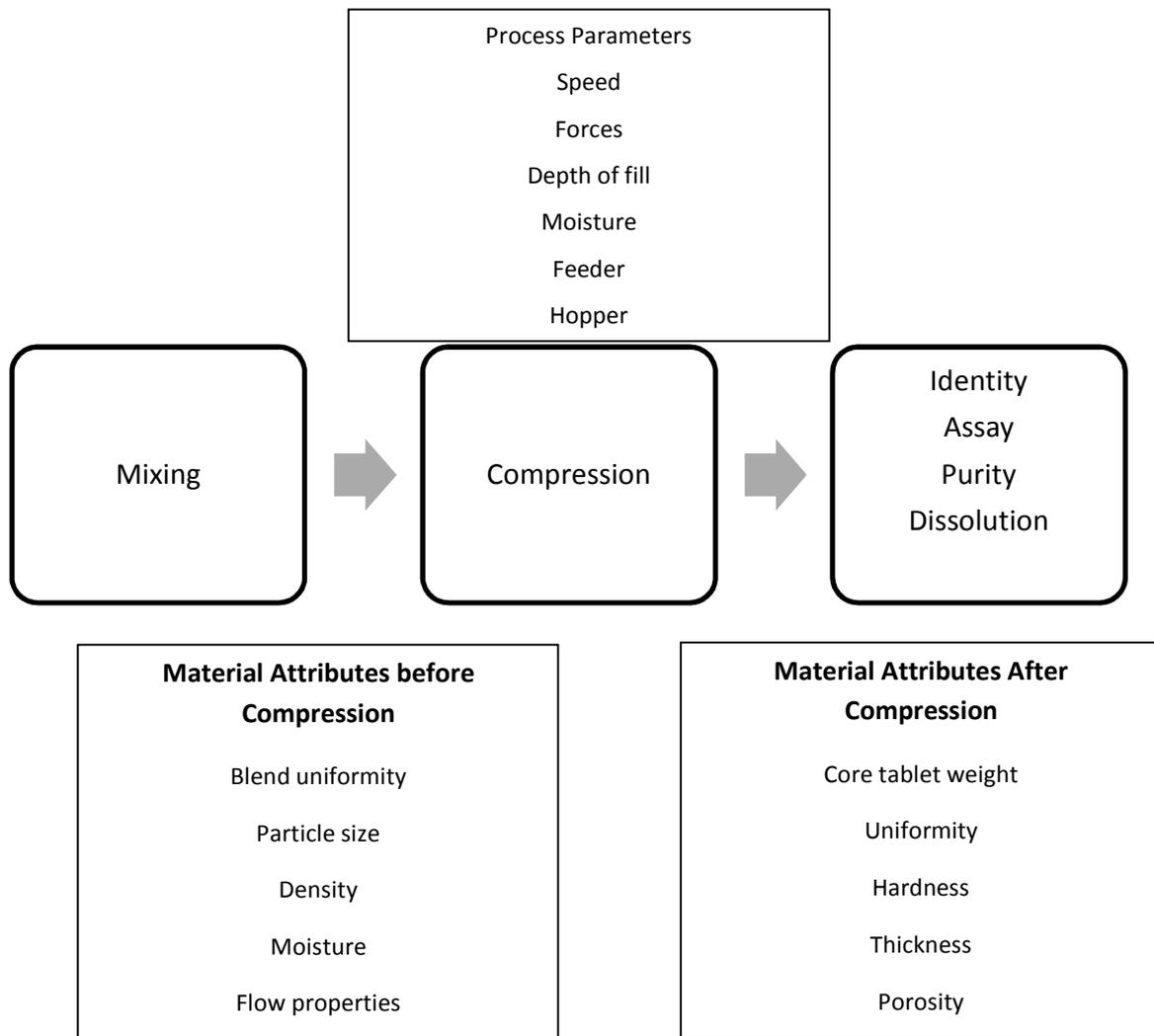
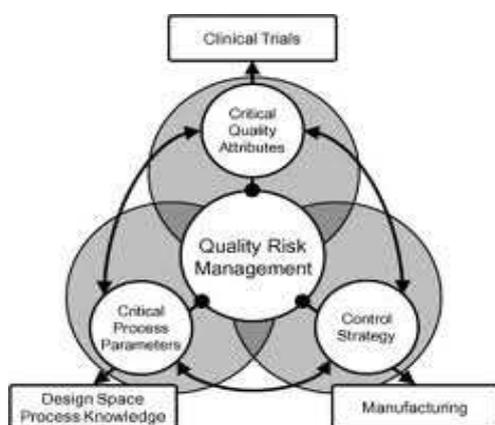


Figure 4 Factors affecting CMAs and CPPs

## Risk Assessment



**Figure 5 Risk assessment process**

According to ICH Q9 guidelines, manufacturing & uses of any drug must possess some risk. Evaluation of risk to quality should be based on scientific knowledge that ultimately links with patient's benefit. The level of effort, formality and documentation of the quality risk management process should be similar with the level of risk. Study of risk assessment helps to decide which parameters of the process are critical & which are not, which guides the establishment of control strategy for in-process, raw material & final testing.

Risk is defined as the combination of probability of occurrence of harm & the severity of harm. Risk assessment is defined

as a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of identification of hazards & the analysis & evaluation of risks associated with exposure to those hazards. Following are the questions that help to risk assessment

- What might go wrong?
- What is the probability it will go wrong?
- What are consequences? Failure modes

To minimize the risk associated with any product, parameters like manufacturing process, quality of raw materials must be thoroughly understood. Also the failure modes should be avoided by selecting proper analytical process, detectability should increase which ultimately leads to decreased consequences.

### Evaluation and quantification of Risk

Probability(P)= Probability of certain failure to occur

Severity(S)= Magnitude of impact of such failure

Detectability(D)= The level or ability to measure such failure

**Risk Priority Number (RPN)= P \* S \* D**

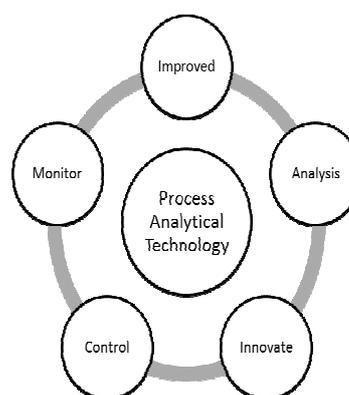
The value of RPN can range from 1 to 125 (for 1 - 5 scale)

### Process Analytical Technology (PAT):

Pharmaceutical development utilised conventional approach which had various disadvantage that if the final product is not matching the specifications then whole batch is to be renewed which cost a lot, another would be if one sample is not matching specification then whole manufacture is to be discarded [8]. To avoid all this problems pharmaceutical industry adapted a new technique PAT that is Process Analytical Technology: A system for designing, analysing and controlling manufacturing through timely measurement for critical and performance attribute of raw material. It demands an understanding over the process which is inculcated during development of drug to reduce a process variation and improve manufacturing capabilities. Its basic goal is to design and develop a process which after every manufacture gives a predefined drug. It identifies all the variation, manages it by using different process and thus overcome it so that the product gets all its characteristic of its initial products<sup>6</sup>. It while

dealing with QbD ensures that process is been carried within Design Space.

1. Product quality and efficiency are achieved by manufacturing analysis
2. Product specifications are based on how formulations and other process affect product performance
3. Quality assurance is continuous
4. Relevant regulatory policies and procedure are accommodated



**Figure 6 Steps involved in PAT**

PAT approach to particle size and control solid state form which allow rapid analysis and control over system. PAT provide a better knowledge of raw materials by characterizing it for both physically and chemically understanding manufacturing process which has got various impact on the product finally made and with all its tools it gives a brand image to a company.

Implementation of Quality by Design:

After discussing various elements & tools of QbD, it is important to know that what exactly stages is involved in the implementation of QbD. The process of implementation occurs mainly in three stages:

### **Stage 1: Method Design**

This stage includes establishing the method performance requirements, developing methods to meet those requirements and then performing appropriate studies to understand the critical method variables that must be controlled to assure the method is robust.

### **Method Performance Requirements**

While utilizing the QbD approach, it is essential at this stage that the sufficient thought should be given to the intended use of the method and that the performance requirements of the method are fully documented. This represents the Analytical Target Profile (ATP) for the method. To build ATP, it is necessary to determine the characteristics that are indicators of method performance. It is important, however not to use ICH Q2 characteristic in the applied process but to

consider method's intended use. Once the important characteristics are defined, next step is to define the target criteria i.e. the most precise & accurate method should be adopted. A key factor in choosing the appropriate criteria is the impact of method variation on the overall manufacturing process capability.

### **Method Development**

Once ATP has been developed & method is decided, it is now important to develop the targeted process. When proper conditions are implemented along with application of improved analytical techniques method is said to be in development process.

### **Method Understanding**

Based on an assessment of risk one can perform an exercise focused on understanding the method. It leads to better understanding of what key input variables might have an impact on the method's performance characteristics. From this, one can identify a set of operational method controls. Experiments can then be run to understand the functional relationship between method input variables and each of the method performance characteristics. Knowledge

obtained during development & at initial stages can be used as an input for risk assessment.

### **Method Design Output**

A set of method conditions will have been developed and defined which are expected to meet the ATP. Those conditions will have been optimized based on an understanding of their impact on method performance.

### **Stage 2 – Method Qualification**

After determining a set of operational method control during design phase, it is necessary to qualify that method along with qualification of equipments. Qualification of method is divided into three stages: method installation qualification (MIQ), method operational qualification (MOQ), and method performance qualification (MPQ).

### **Method Installation Qualification**

It includes performing a “method walkthrough” exercise with both the development and routine analytical teams. After qualification of design space & equipments it is important to convey all the knowledge about process, method conditions & operating controls to the

analyst. Pre-existing knowledge can be used for MIQ.

### **Method Operational Qualification**

It is focused on ensuring whether method meets its design intent or not and demonstrating that the method meets the specific requirements that have been pre-defined in the Analytical Target Profile. A fundamental principle of this phase is that it should be built on the information which already has been generated during the experiments those are previously performed.

### **Method Performance Qualification**

At this stage, the actual manufactured supply samples are tested in facility, equipment and by personnel that will be used for routine analysis. The method should be operated exactly in accordance with the defined method controls and local operating procedures.

### **Stage 3 - Continued Method Verification**

The main objective of this stage is to assure that the applied method remains in the controlled state. It may include the collection & analysis of data that relates to the method performance - for instance, by setting criteria for replication of sample.

Attention should also be given to any out of specification (OOS) or out of trend (OOT) results generated by the method after it is being implemented in the routine environment.

During lifecycle of a product, both the manufacturing and method implemented are likely to experience a number of changes brought through unintentional deviations and that needs to be continually improved. All the changes occurred in method must be properly understood in the light of knowledge. When there is a need to change the environment, method qualification should be revised. Even after requalification of method there may be a need to generate a new ATP for the method for consistent and reliable results. Consistent with QbD principles, the extent of requalification should be driven by scientific principles.

## **CONCLUSIONS**

Quality by Design has brought a systematic way to develop an inbuilt quality in a drug along with robustness of a development process. All the elements and tools of QbD allow analyst to set a desired target for product's quality and to achieve it. The

elements of QbD includes Target product quality profile, Critical quality attributes, critical material attributes, critical process parameter, were as tools of QbD are design of experiment, risk assessment, process analytical techniques.

## **REFERENCES**

1. Anurag SR and Helen W: Quality by design for biopharmaceuticals. *Nature Biotechnology* 2009; 27: 26-34.
2. Bhagyesh T: Quality by Design (QbD) in pharmaceuticals. *International Journal of Pharmacy and Pharmaceutical Science* 2012; 1: 17-29.
3. Premchandani TA and Barik BB: Quality by Design (QBD): A tool for quality improvement. *Journal of Advances in Pharmacy and Health Research* 2011; 1: 7-10.
4. Sandipan R: Quality by design: A holistic concept of building quality in pharmaceuticals. *International Journal of Pharmaceutical and Biomedical Research* 2012; 3: 100-108
5. Alex E, Pascal V, Thomas S, Herve B, Ralf G, Claire LES and James S: Application of

quality by design approach to the drug substances manufacturing process of an Fc fusion protein: Towards a global multistep design space. *Journal of Pharmaceutical Science* 2012; 101: 3604-3618.

6. Bryan SR and Xuhong Li: Quality by Design and Process Analytical Technology for Sterile Products. *AAPS PharmSciTech* 2011; 12: 114-118.

7. Wu H, White M and Khan MA: Quality by Design: An integrated process analytical technology for a dynamic pharmaceutical co-precipitation process characterization and process design space development.

*International Journal of Pharmacy* 2011; 405: 63-78.

8. Robert AL, Sau LL, Laiming L, Andre R and Lawrence XYu: Quality by design: Concept for ANDAs. *AAPS Journal* 2008; 10: 268-276.

9. Adam S, Suzzi D, Radeke C and Khinast JG: An integrated Quality by Design (QbD) approach design space definition of a blending unit operation by Discrete Element Method (DEM) simulation. *European Journal of Pharmaceutical Science* 2011; 42: 106-115.