Available online at www.ijpab.com

ISSN: 2320 – 7051
Int. J. Pure App. Biosci. **2 (5):** 214-223 (2014)

Review Article

INTERNATIONAL JOURNAL OF PURE & APPLIED BIOSCIENCE

Quality by Design (QBD) Approach used in Development of Pharmaceuticals

Jyotsna Balasaheb Jadhav[1]*, Nitin NamdeoGirawale[2] and Rakesh Ashok Chaudhari[3]
Department of Quality Assurance Techniques, M.V.P. Samaj's College of Pharmacy, Near K.T.H.M. Campus, Gangapur road, Nashik-422002, Maharashtra, India
*Corresponding Author E-mail: jassijadhav306@gmail.com

ABSTRACT

Recent pharmaceutical regulatory documents have stressed the critical importance of applying quality by design (QbD) principles for in-depth process understanding to ensure that product quality is built in by design.The purpose of this paper is to discuss the pharmaceutical Quality by Design (QbD) and describe how it can be used to ensure pharmaceutical quality. Quality cannot be tested into products but quality should be built in by design.

Under this concept of QbD throughout designing and development of a product, it is essential to define desire product performance profile [Target product profile (TPP), Target product Quality profile(TPQP) and identify Critical quality attributed (CQA). On the basis of this we can design the product formulation and the process to meet the product attributes. These leads to recognize the impact of raw material [Critical material attributes (CMA), Critical process parameter (CPP), on the CQA's and identification and source of variability.The application of the concept of quality by design (QbD) presented in this paper aligns with the principles of ICH Q8, Q9 and Q10 guidelines.

Key words: *Quality by Design (QbD), Quality target product profile (QTPP), Critical process parameter (CPP), critical quality attribute (CQA), Target product profile (TPP), and Critical material attributes (CMA).*

INTRODUCTION

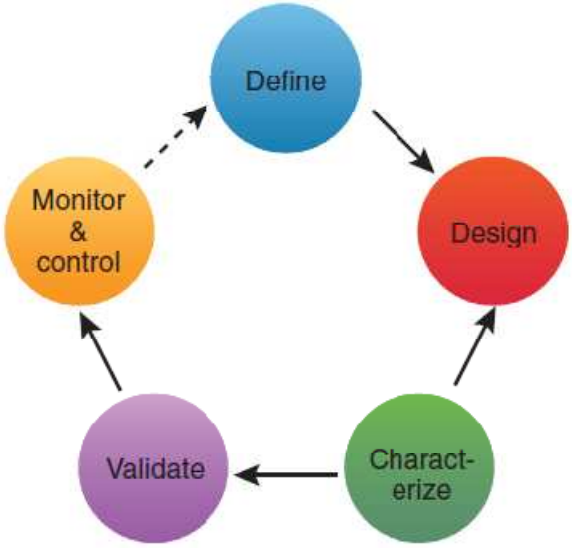
Quality by design (QbD) encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications. The concept of quality by design (QbD) has been recently adopted in the pharmaceutical industry through several initiatives {e.g., ICH Q8[1], Q9[2]and Q10[3], and the new regulatory documents, Process Analytical Technology (PAT)[5], FDAs cGMP for the 21st Century[4]}. The general aim is to switch from the quality by testing (QbT) paradigm previously implemented in the pharmaceutical industry to a development aimed at improving the understanding of the processes and the products and hence improving product quality, process efficiency and regulatory flexibility.

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of theproduct. The information and knowledge gained from pharmaceutical developmentstudies and manufacturing experience provide scientific understanding to support theestablishment of the design space, specifications, and manufacturing controls.Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that qualitycannot be tested into products; i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful.

The Pharmaceutical Development section should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use. This section should include sufficient information in each part to provide an understanding of the development of the drug product and its manufacturing process[1].

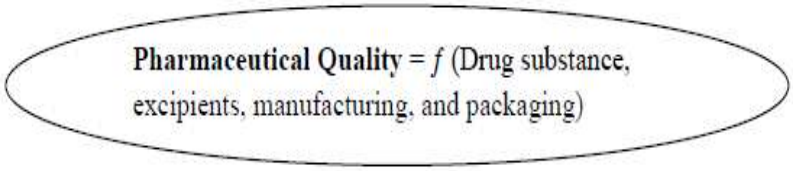
The Food and Drug Administration (FDA) Office of Generic Drugs (OGD) has developed a question basedreview (QbR) for its chemistry, manufacturing and controls (CMC) evaluation of Abbreviated New Drug Applications (ANDAs). QbR is a new quality attributes. It is a practical implementation of some underlying concepts and principles outlined by the FDA's Pharmaceutical CGMPs for the twenty first century and quality by design (QbD) initiatives[6]. Figure 1, which illustrates the different phases during the life cycle of a pharmaceutical process: define, design, characterize, validate, and monitor and control. The final link between "monitor and control" and "define" represents process changes that are initiated based on process improvement opportunities identified during process monitoring or introduced otherwise to improve process performance or robustness[7]. Changes originating in this manner would again go through the cycle illustrated in Fig. 1.

Fig. 1: Illustration of the different steps in development of a pharmaceutical product.
Pharmaceutical Quality by Design



Pharmaceutical Quality by Design

ICH Q8 defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity. "ICH Q8 guideline states that Quality by Design 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".[1]



ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are foundation of QbD (Fig. 2)[8]

"Product testing alone is not sufficient to assure that a process consistently produces a product with predetermined specifications. Adequate process design; knowledge and control of factors that produce process variability and successful validation studies, in conjunction with product testing, provide assurance that the process will produce a product with the required quality characteristics".

Fig. 2: The Foundation of QbD

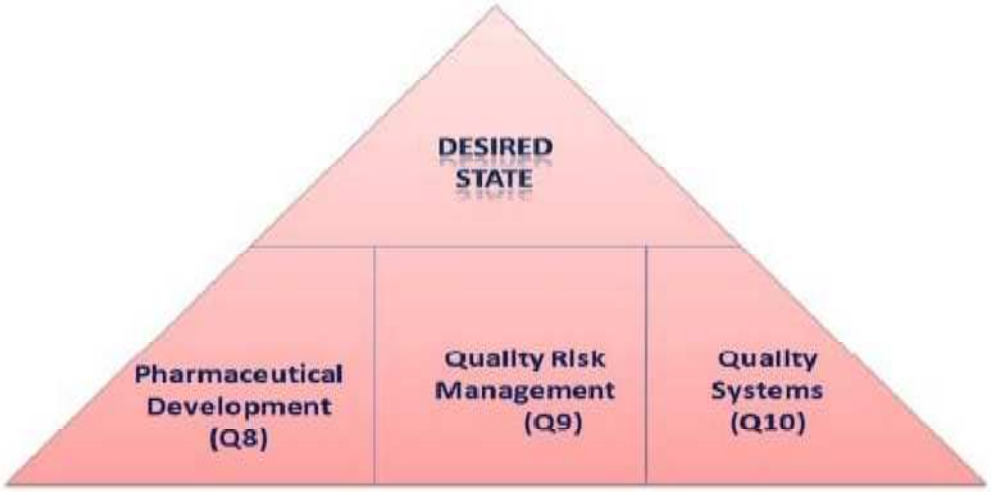


Table 1: Comparison: QbT and QbD approach[9]

Elements	QbT approach	QbD approach
Product process development	Data intensive submission disjointed information without big picture. A specification based on batch history. Frozen process‟-discouraging changes. Focus on reproducibility-often avoiding or ignoring variation Focus on reproducibility-often avoiding or ignoring variation.	Knowledge rich submission- showing product knowledge and process. A specification based on product performance requirement understanding. Flexible process within the design space allowing continuous improvement. Focus on robustness-Understanding and controlling variations.
Risk management	Compliance focus changes require prior approval. Control strategy managed mainly by intermediate & end product testing. Quality decision divorced from science & risk evaluation.	Regulatory scrutiny adjusted to the level of process understanding continuous improvement allowed within the design space. Risk based; control shifted up strong real-time release. 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. Quality assured by testing & inspection.	Management of variability process control focused on critical attributes, continuous quality verification. 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.

KEY ASPECTS OF QBD INCLUDE

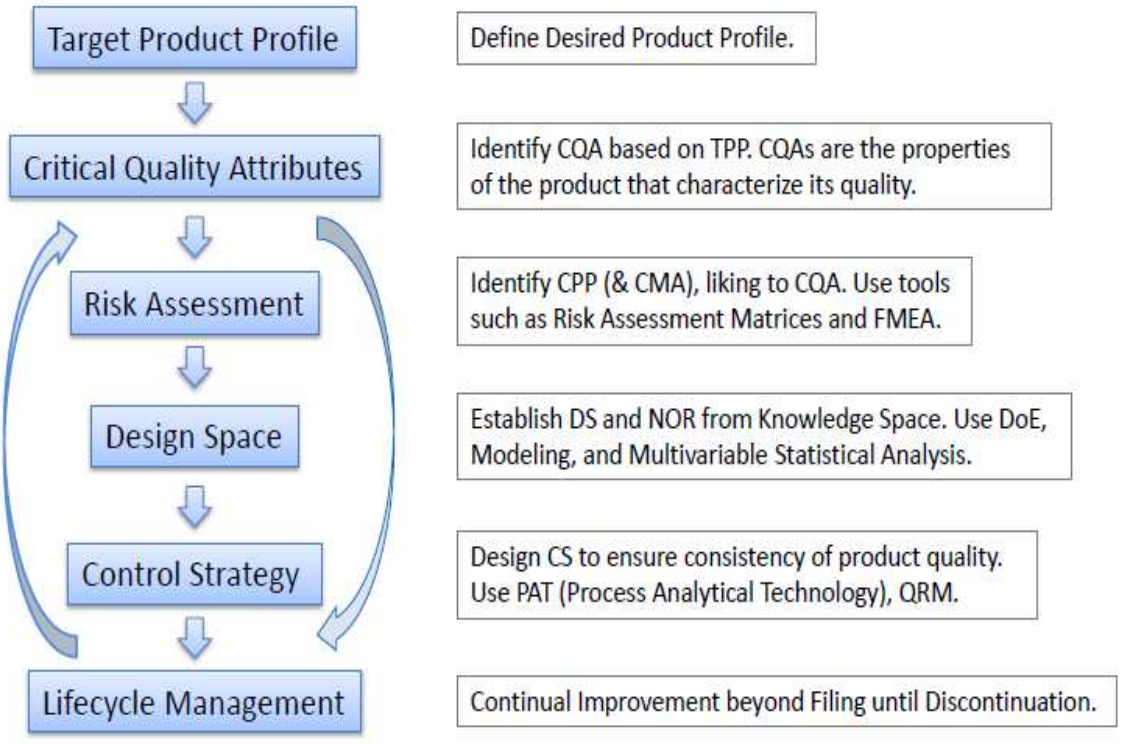
1] The Target Product Quality Profile (TPQP)

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, andthus the safety and efficacy, of a drug product is realized". This includes dosage formand route of administration, dosage form strength(s), therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed and drug product-quality criteria (e.g. sterility and purity) appropriate for the intended marketed product. The concept of TPP in this form and its application is novel in the QbD paradigm[4].

TPP forms the basis for product design in the following way[10].

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

Fig. 3: Elements of Pharmaceutical Development (ICH Q8R2)

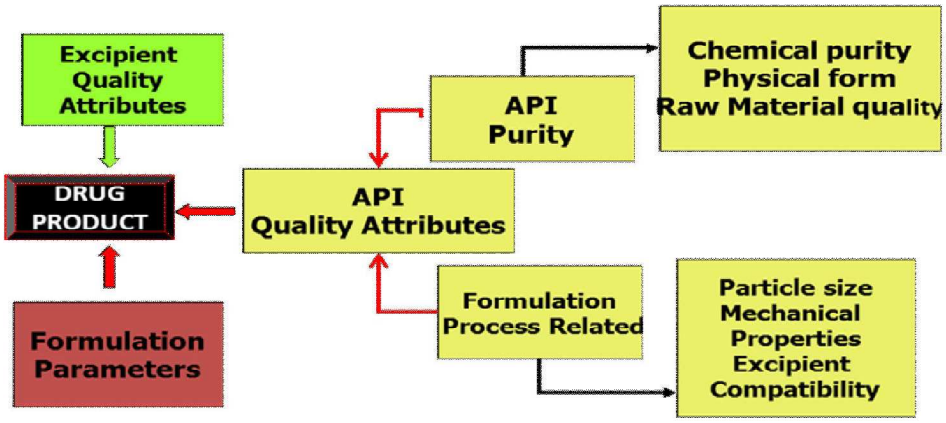


2] Critical Quality Attribute

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 an appropriate limit, range, or distributed to ensure the desired product quality" Identification of CQAs is done through risk assessment as per the ICH guidance Q9. Prior product knowledge, such as the accumulated laboratory, nonclinical and clinical experience with a specific product-quality attribute, is the key in making these risk assessments. Such knowledge may also include relevant data from similar molecules and data from literature references.

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. CQAs for other delivery systems can additionallyinclude more product specific aspects, such as aerodynamic properties for inhaledproducts, sterility for parenteral, and adhesion properties for transdermal patches.For drug substances, raw materials and intermediates, the CQAs can additionallyinclude those properties (e.g., particle size distribution, bulk density) that affect drugproduct CQAs[1,11].

Fig.4: Role of (CQA)



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 theability of a process to demonstrate acceptable quality andperformance and tolerate variability in inputs at the sametime. To demonstrate the reproducibility and consistencyof a process, process capability should be studied. Processcapability is a statistical measure of the inherent processvariability for a given characteristics. The most widelyaccepted formula for process capability is six sigma.Process capability index is the value of the tolerancespecified for a particular characteristic divided by the processcapability, which is defined as follows:

$$\text{Process capability index (CpK)} = \frac{\text{Upper limit of specification - Lower limit ofspecification}}{6 \text{ standard deviation}}$$

If the CpK is significantly greater than one, the process isdefined capable. If the process capability is low, there are five step procedures toprogressively reduce the variability of the process. These fivesteps are:

I. Define: The intended improvement should be clearlystated

II. Measure: The critical product performance attributesshould be measured to see if they are out ofspecification and used to the sigma level of the process.

III. Analyze: When the sigma level is below the target, stepsshould be taken to increase it, starting by identifying themost significant causes of the excessive variability.

IV. Improve: The process should be redesigned and/ orprocess controls should be incorporated to eliminate orattenuate the significant toot causes of variance.

V. Control: The improved manufacturing process shouldbe evaluated and maintained[12,13].

4] Risk Assesment

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).

QRA is a science based process that can aid identification of CPPs and thus eliminating risk, resulting in high confidence that the analytical method will meet the QTTP under all conditions of use. Thus, a large number of parameters can actually be safely eliminated by use of QRA tools, for example failure mode effects analysis (FMEA) and Ishikawa diagrams on the basis of prior knowledge and initialexperimentation. In FMEA the variables are ranked on the basis of the likelihood failure will occur (probability), affect on the pharmaceutical results (severity), and difficulty of detection (detectability), resulting in a risk priority number (RPN). Factors with an RPN above a cut-off level can then be evaluated by subsequent studies whereas factors with a lower RPN can be eliminated from further study[2].

Ishikawa diagrams segregate risks into different categories, for example those associated with instrumentation, materials, methods, measurements, laboratory climate, and human factors. Fig. 6 indicate the Fishbone Diagram forblending unit operation. A fault tree analysis is used to link the potentially critical quality attribute "content uniformity" to a potential failure mode and potential causes, as outlined in Fig.5. Four main causes, i.e., raw and intermediate material properties, processing parameters, equipmentand design parameters as well as environmental factors, and the associated sub-causes were identified and afterwards systematically listed in an Ishikawa diagram Fig. 6.[14]

Fig. 5: Risk identification: fault tree analysis of variable content uniformity

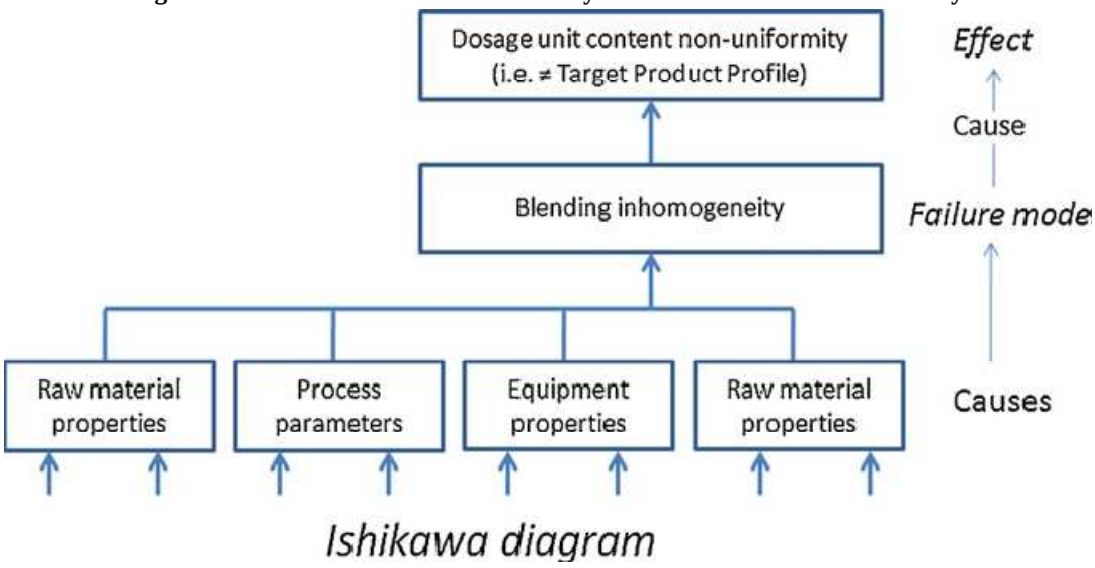
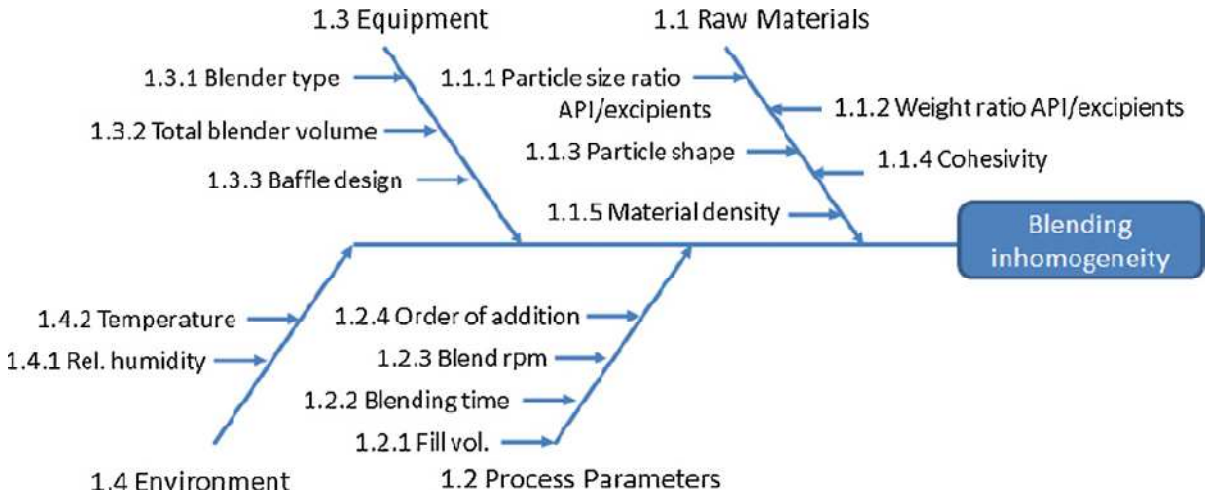


Fig. 6: Risk identification: Ishikawa diagram for the blending unit operation

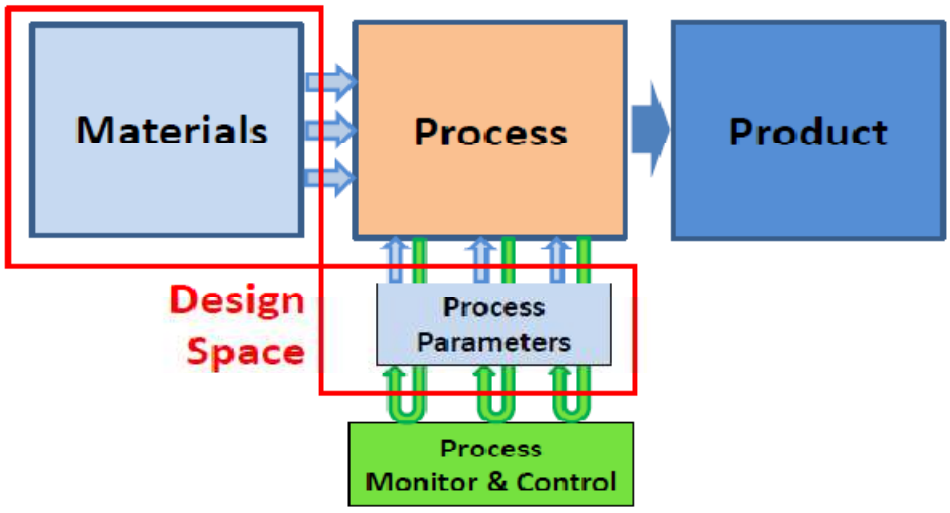


5] Design Space

TheICH Q8(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[1].

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.

Fig. 7: Design space



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. ICH Q8(R2).

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. The control strategy can include the following elements: procedural controls, inprocess controls, lot release testing, process monitoring, characterization testing, comparability testing and stability testing[16].

Particularly, the control strategy may include:

- Control of raw material attributes (e.g., drug substance, excipients and primary packaging materials) based on an understanding of their impact on process-ability or product quality.
- Product specifications
- Procedural controls
- Facility controls such as utilities, environmental systems and operating conditions Controls for unit operations that have an impact on downstream processing or end-product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution)[9].

7] Life Cycle Management

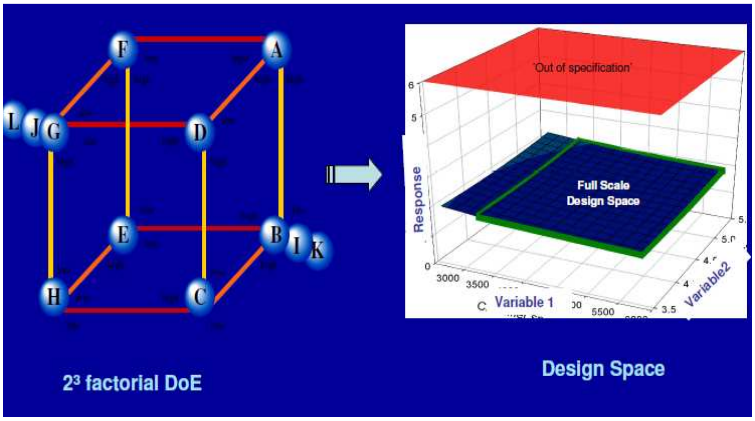
In the QbD paradigm, process changes within the design space will not require review or approval. Therefore, process improvements during the product life cycle with regard to process consistency and throughput could take place with fewer post approvalsubmissions. In addition to regulatory flexibility, the enhanced understanding of themanufacturing process would allow more informed risk assessment as per ICH Q9 regarding the affects of process changes and manufacturing deviations (excursions) on product quality[1,2, 11].

TOOLS OF QUALITY BY DESIGN

I] 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. As each unit operation has many input and output variables as well as process parameters, it is impossible to experimentally investigate all of them. DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those who do not, as well as details such as the existence of interactions and synergies between factors as in Figure 8, Design of experiments[17, 18].

Fig. 8: Design of experiment (DOE)



II] 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.” The design space is defined by the key and critical process parameters identified from process characterization studies and their acceptable ranges. These parameters are the primary focus of on-, in- or at-line PAT applications. In principle, real-time PAT assessments could provide the basis for continuous feedback and result in improved process robustness. NIR act as a tool for PAT and useful in the RTRT (Real Time Release Testing) as it monitors the particle size, blend uniformity, granulation, content uniformity, polymorphism , dissolution and monitoring the process online, at the line and offline, thus it reduces the release testing of the product[5]

III] 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. The early list of potential parameters can be fairly broad, but can be modified and prioritized by additional studies (e.g., through a combination of design of experiments, mechanistic models). Once the considerable parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding.

The pharmaceutical industry and regulators can evaluate and manage risks by using well-known risk management tools and/ or internal procedures such as,

• Basic risk management facilitation methods (flowcharts, check sheets etc.);
• Failure Mode Effects Analysis (FMEA);
• Failure Mode, Effects and Criticality Analysis (FMECA);
• Fault Tree Analysis (FTA);
• Hazard Analysis and Critical Control Points (HACCP);
• Preliminary Hazard Analysis (PHA);
• Risk ranking and filtering; [19]

CONCLUSION

Quality by design is an essential part of the modern approach to pharmaceutical quality. This is a concept that can and is replacing the traditional approach, and is firmly taking roots in the industry. QbD, if properly implemented and taken together with the current world wide harmonization of regulations and risk should be taken for what it has to offer, rather than what its concerns. This paper describes the emphasis on the importance of the Quality Target Product Profile in articulating a quantitative performance target for QbD, identification of critical material attributes that provide a mechanistic link of the product quality to the manufacturing process, clarification that critical process parameters are operating parameters and should be combined with critical material attributes to describe the relation between unit operation inputs and outputs, the role of the control strategy as the mechanism for incremental implementation of QbD elements into practice. QbD is the future of product and process improvement, and as such leads to continuous improvement and innovation in products and processes.

REFERENCES

1. ICH Q8 (R2), Pharmaceutical Development, Part I: Pharmaceutical Development, (2009)
2. ICH Q9, Quality Risk Management, (2005)
3. ICH Q10, Pharmaceutical Quality Systems, (2008)
4. 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)
5. US Food and Drug Administration (FDA), Guidance for industry PAT-A framework for innovative pharmaceutical manufacturing and quality assurance, FDA, Washington, DC, USA, (2004)
6. Lawrence, X. Raw, A.Lionberger, R. Rajagopalan, R. Lee, L. etal. U.S. FDA question-based review for generic drugs: A new pharmaceutical quality assessment system, *J. Generic Med.*, **4**:239–248 (2007)
7. Rathore, A.S. Winkle, H. Quality by design for biopharmaceuticals, *Nat Biotechnol.*, **27**: 27- 34 (2009)
8. 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.*, **17**: 20-28(2012)
9. Gawade, A. Chemate, S. Kuchekar, A. Pharmaceutical Quality by Design: A New Approach in Product Development. *Res Rev: J Pharm. Pharm Sci.*, **2**: 5-12 (2013)
10. Juran, J.M. Juran on quality by design The new steps for planing quality into goods and services, Revised Edition, free press, newyork, 1992,1-2
11. Purohit, P.J. Shah, K.V. Quality By Design (Qbd): New Parameter For Quality Improvement & Pharmaceutical Drug Development,*Pharma Science MonitorInt J Pharm Sci*.,**4**: 1-19 (2013)
12. Roy, S. Quality by design: A holistic concept of building quality in pharmaceuticals, *Int J Pharm Biomed Res*., **3**: 100-108 (2012)
13. Glodek, M. Liebowitz, S. McCarthy, R. McNally, G. Oksanen, C. Schultz, T. *et al. Pharm. Eng.*, **26**: 1-11 (2006)
14. Siegfried, A.Suzzia,D.Radekea, C.Khinasta, J.G. 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*.,**42**: 106–115 (2011)

15. Nwoko,V.E. Quality By Design (Qbd): Manufacturing And Product Quality Ofgenerics Drugs Perspective, *J Glob Tre Pharm Sci*., **4**: 1257-1262 (2013)
16. Shajeeya, A.S. Viswanath, A. Srinivasa, P. Quality By Design - Novelty In Pharmaceuticals, *World J Pharma Res*., **2**: 1409-1422 (2013)
17. Shah, R.B. Quality by Design in Pharmaceutical Manufacturing, U.S. Food and Drug Administration (2009)
18. Bhasin, R.Ghosh, P. Design and development of ondansetron orally disintegrating tablets and its optimization using design of experiment, *Int J Pharm Sci Res.*,**3**: 840-847 (2012)
19. Ian House Process Understanding: for Scale-up and Manufacturing method of Active Ingredients, First edition, Wiley-VCH Ver lag GMb H&Co. KGaA (2011)