



INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

QUALITY BY DESIGN (QBD): NEW PARAMETER FOR QUALITY IMPROVEMENT & PHARMACEUTICAL DRUG DEVELOPMENT

HRUSHIKESH L. KORLA, P. J. PUROHIT, GHANSHYAM PATEL.

Arihant School of Pharmacy & Bio Research Institute, Gujarat, India.

Accepted Date: 19/04/2014; Published Date: 27/04/2014

Abstract: The purpose of above article is to discuss the concept of pharmaceutical Quality by Design (QbD) and describe how it can be help to ensure pharmaceutical quality & drug development. Quality by design is an essential part of the modern approach to pharmaceutical quality. QbD has become the answer to assist both industry and FDA to move towards a more scientific, risk based, holistic and proactive approach to pharmaceutical development. The elements of quality by design are examined and a consistent nomenclature for quality by design, critical quality attribute, critical process parameter, critical material attribute, and control strategy is proposed. The QbD is a systemic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure product quality according to requirement. Implementation of QbD is enabling transformation of the chemistry, manufacturing, and controls review of Abbreviated New Drug Applications (ANDAs) into a modern, science and risk based pharmaceutical quality assessment. .. A new approach to drug development could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product's life cycle.

Keywords: Quality by design, Quality Risk Management, element of Quality by Design, critical quality attributes, Control Strategy, Design space



PAPER-QR CODE

Corresponding Author: MR. HRUSHIKESH L. KORLA

Access Online On:

www.ijprbs.com

How to Cite This Article:

Hrushikesh Korla, IJPRBS, 2014; Volume 3(2): 608-624

INTRODUCTION

Definition: 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⁾

Quality :

Definition: Totality of features and characteristics of a product or services that bear on its ability to stated and implied needs.⁽²⁾

Design :

Definition: refers to a plan or convention for construction of an object or a system.⁽²⁾

QBD is a customer oriented piece of work, which defines and control risk, creates reliable knowledge & achieves optimum outcomes, by using facts, multifunctional teamwork & systematic methods to manage the process & decisions, helps in meeting regulatory requirements, robustly method development, meet commercial & quality performance targets, & quality products for customers (Juran,1992).⁽³⁾

Over the past few years, pharmaceutical companies have been facing an increasingly difficult economic climate. An increase in the regulatory hurdles for the approval of new molecular entities, patent expirations and increased healthcare costs have resulted in more focus in the costs associated with the manufacturing and development of pharmaceutical.⁽⁴⁾

In mid 2002, in U.S. Food and Drug Administration (FDA) published a concept paper on current good manufacturing practice for 21th century. This document expressed desire that companies build safety, quality and efficacy into their new pharmaceutical products as early as possible. This concept known as Quality by Design⁽⁵⁾

The holistic and systematic approach of QbD was relatively new to the pharmaceutical industry at the beginning of the twenty-first century. However, elements of QbD were certainly being applied across the industry long before then. QbD was put into practice in a big way with the advent of the FDA CMC pilot program in 2005. Nine companies participated in the program and eventually submitted regulatory filings based on a QbD framework [1, 2, 5-7].⁽⁶⁾

In addition to this new concept being considered by FDA in its cGMP initiative, two important guidance documents were published as part of International Conference on Harmonization (ICH) guidelines: Q8 Pharmaceutical Development and Q9 Quality Risk Management.⁽⁷⁾

Table-1: QbD: Regulatory tools⁽⁷⁾

Date	Guidline reference	Scope
Aug 2009	ICH Q8	Pharmaceutical development
Nov 2005	ICH Q9	Quality risk management
Jun 2008	ICH Q10	Pharmaceutical quality system
Jan 2011	FDA	Process validation. General principal and practices
Dec 2011	ICH Q8/Q9/Q10	Guide for implementation
March 2012	EMA/CHMP/QWP/811210	Real time release testing
March 2012	EMA/CHMP/QWP/CVMP/70287 (draft)	Process validation
May 2012	ICH Q11	Development and manufacture of Drug substance

Why QBD⁽⁸⁾

- Higher level of assurance of product quality
- Cost saving and efficiency for industry and regulators
 - Facilitate innovation to address unmet medical needs
 - Increase efficiency of manufacturing process and reduce manufacturing cost and product rejects
 - Minimize potential compliance actions, costly penalties and recalls
 - Enhance opportunities for first cycle approval
 - Streamline post approval manufacturing changes and regulatory processes
 - More focused PAI and post approval cGMP inspections
 - Opportunities for continual improvement

Benefits of QbD:

1. Improves information in regulatory submissions⁽⁹⁾
2. Improves quality of review (establishing a QMS for CMC)⁽⁹⁾
3. Ensures better design of products with less problems in manufacturing⁽⁹⁾
4. Improves interaction with FDA –deal on a science level instead of on a process level.⁽⁸⁾
5. Allows for better understanding of how APIs and excipients affect manufacturing⁽⁹⁾
6. Reduce Product Variability⁽⁸⁾
7. Regulatory flexibility⁽¹⁰⁾
8. Manage product lifecycle, including continual improvement.
9. Innovation and Improvement encourage the use of new technologies which accelerate the change and enable a proactive product lifecycle marketing plan.⁽¹¹⁾
10. Improve product reliability and reproducibility.⁽¹¹⁾
11. The product can be consistently produced without batch to batch variations.



FDA's view on QbD, Moheb Nasr, 2006

6

Figure-1:FDA's view on QbD⁽⁹⁾

Table-2 Comparison of the current state to the future desired QbD state.

Aspect	Current state	Desired QbD state
Pharmaceutical development	Empirical; typically univariate experiments	Systematic; multivariate experiments
Manufacturing process	Locked down; validation on three batches; focus on reproducibility	Adjustable within design space; continuous verification within design space; focus on control strategy
Process control	In-process testing for go/no-go; offline analysis	PAT utilized for feedback and feed forward in real time
Product specification	Primary means of quality control; based on batch data	Part of overall quality control strategy; based on product performance
Control strategy	Mainly by intermediate and end product testing	Risk-based; controls shifted upstream; real-time release
Lifecycle management	Reactive to problems and OOS; postapproval changes Needed	Continual improvement enabled within design space

A comparison of the “current state” to the future “desired state” was succinctly summarized by Nasr in Table-2⁽⁶⁾

Quality risk management :

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.⁽¹²⁾

The quality risk management system should ensure that :

- The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient.
- The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.⁽¹²⁾

Quality risk management (QRM) is a key enabler for the development and application of QbD.⁽³⁾ ICH Q9 Quality Risk Management indicates that, the manufacturing and use of a drug product necessarily entail some degree of risk.^(13&14) central in Quality by design in product lifespan is relying upon risk management techniques to make decision. Good risk

management decision rely upon the knowledge you gain through the product development phase into full scale manufacturing.⁽⁸⁾

Risk assessments are often driven by knowledge gaps or uncertainty. Study results determine which variables are critical and which are not, which then guide the establishment of the control strategy for in process, raw material and final testing.⁽¹³⁾

It is one of the tools that provide a proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality. It is a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, processes, and components. (3) Prior knowledge comprises previous experience and understanding of what has been successful or unsuccessful, and recognition of issues, problems, or risks.⁽¹⁵⁾

An effective quality risk management approach can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing.⁽¹⁵⁾

General Quality Risk Management Process:

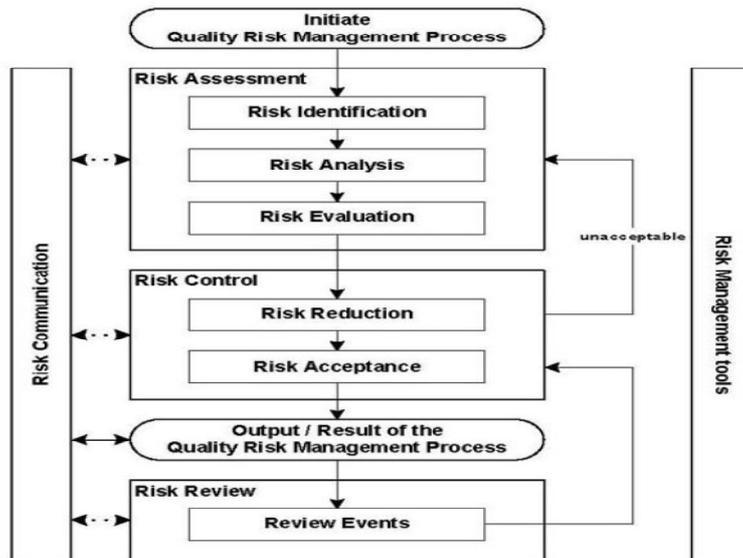


Figure 2: Overview of a typical quality risk management process⁽¹²⁾

A. Responsibilities :

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. Decision makers should:

- Take responsibility for coordinating quality risk management across various functions and departments of their organization and
- Ensure that a quality risk management process is defined, deployed, and reviewed and that adequate resources are available.⁽¹⁶⁾

B. Initiating Process :^(12&16)

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. The process might include the following:

- Define the problem or risk question, including pertinent assumption side notifying the potential for risk.
- Assemble background information or data on the potential hazard, harm or human health impact relevant to the risk assessment.
- Identify a leader and critical resources.
- Specify a timeline, deliverables, and appropriate level of decision making for the risk management process.

C. Risk Assessment:⁽¹⁶⁾

Risk assessment consists of the identification of hazards and the analysis assessments begin with a well-defined problem description or risk question.

- **Risk identification:** Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description.
- **Risk analysis:** Risk analysis is the estimation of the risk associated with the identified hazards.
- **Risk evaluation:** Risk evaluation compares the identified and analyzed risk against given risk criteria.

Role of the Quality Risk Management in QbD:⁽¹⁵⁾

ICH Q9 discuss the role of risk management in pharmaceutical development as follow

1. To select the optimal product design (e.g. parenteral concentration vs. pre mix) and process design (e.g. manufacturing technique vs aseptic process)

2. Enhance enhance knowledge of product performance over a wide range of material attributes (particle size distribution, moisture content, flow properties) processing option and process parameters.
3. To assess the critical attributes raw materials, solvent, Active Pharmaceutica Ingredient (API)- starting materials, API's excepients, or package materials.

Risk management should:⁽¹⁷⁾

- Creat value
- Be a integral part of oaganizational processes
- Be a part of decision making
- Be systematic and structured
- Be based on the best available information
- Be tailored
- Take into account human factor
- Be transparent and inclusive
- Be dynamic, iterative and responsive to change
- Be capable of continual improvement and enhancement

Regulatory requirement:⁽¹⁷⁾

Following are the regulatory guidelines for the quality risk management :

- International Conference Harmonization (ICH) Q9 – Quality RiskManagement
- European Medicines Agency (EMA)
 - Eudralex – Volume 4, Good Manufacturing Practice (GMP) Guideline
- FDA
 - Guidance for Industry – Q9 Quality Risk Management

The greatest benefits come from using the principles described in ICHQ8, Q9 & Q10 together to provide an integrated approach to reducing risk, based on science. Quality Risk Management

(QRM) is a systematic process for the assessment, control, communication & review of risks to quality of the drug product across the product lifecycle.⁽¹⁷⁾

The FDA defines a Risk Management Program (RMP) as, "a strategic safety program designed to decrease product risk by using one or more interventions or tools. The RMP for moderate to severe risks should be reviewed and updated more frequently than less than those have a lower evaluation."⁽¹²⁾

Table-3

FDA Guideline	RMP Elements
Learning about and interpreting a products benefits and risks	<ul style="list-style-type: none"> • Risk and Issue Management • Strategy • Risk Identification Technique • Risk Evaluation Technique
Designing and Implementing Interventions	<ul style="list-style-type: none"> • Risk Response Planning • Risk and Issue Management Plan
Evaluating and Revising Interventions	Risk and Issue Management Plan

Element of Quality by design:^{(2)(18&19)}

The element of QbD are describe in the followig figure

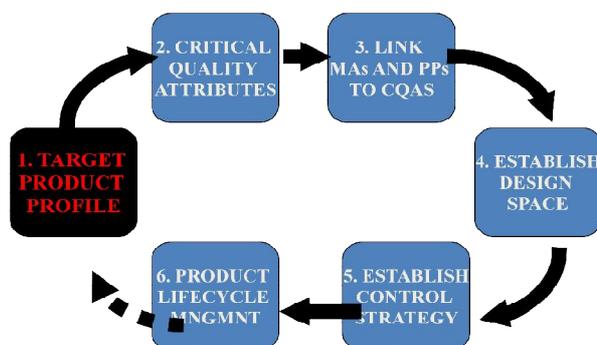


Figure-3: Elements ofQbD

1. Target product profile (TPP) :

The target product profile (TPP) 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, of a drug product is realized”⁽²⁰⁾.

This includes dosage form and 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.⁽⁴⁾

The TPP guides formulation scientists to establish formulation strategies and keep formulation efforts focused and efficient. TPP is related to identity, assay, dosage form, purity, stability in the label⁽⁷⁾.

“The TPP provides a statement of the overall intent of the drug development program, and gives information about the drug at a particular time in development. Usually, the TPP is organized according to the key sections in the drug labeling and links drug development activities to specific concepts intended for inclusion in the drug labeling.”

TPP forms the basis for product design in the following way^{(2)(3&18)}

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

2. Critical quality attributes (CQA) :

A critical quality attribute is 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.^(7&20). 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.⁽²⁾

In addition to defining the requirements to design the product, the QTPP will help identify critical quality attributes such as potency, purity, bioavailability or pharmacokinetic profile, shelf-life, and sensory properties.⁽⁶⁾

Critical quality attributes (CQA) contain following parameters⁽²⁰⁾:

- Appearance
- Particle size
- Morphic forms
- Water content
- Residual solvents
- Organic impurities
- Assay
- Inorganic impurities
- i. Heavy metals
- ii. Residue on ignition

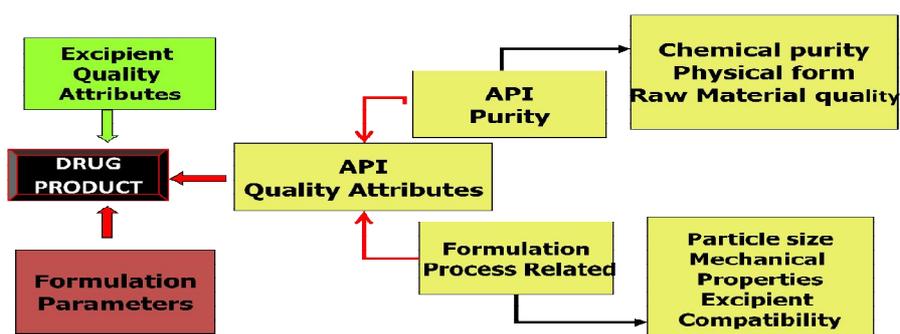


Figure-4: Role of (CQA)⁽²⁾

3. Design space :

Definition : "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality".^(21&22) The relationship between the process inputs (material attributes and process parameters) and the critical quality attributes can be described in the design space⁽²¹⁾

The DS is necessarily encompassed within the experimental domain, which is the multidimensional space formed by the factor ranges used during method development.⁽²²⁾ Change during design space do not require regulatory review or approval.⁽⁶⁾ The design space for a unit operation or process step encompasses the acceptable ranges for the critical process parameters of this step that will deliver product of the desired quality.⁽⁶⁾

Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. proposed by the applicant and is subject to regulatory assessment and approval.⁽²¹⁾ The applicant can choose to establish independent design spaces for one or more unit operations, or to establish a single design space that spans multiple operations.⁽²²⁾

It's a Key for claiming Process understanding (pharmaqbd.com, 2011), which establishes a link between the attributes of the drug product and process parameters, process attributes and material attributes of the active pharmaceutical ingredient (API) and excipients that go into the drug product.⁽³⁾

In some cases, boundaries will be identified that are known to be an *edge of failure*. In these situations, it may be important to set boundaries at acceptable tolerance intervals around the edges of failure to better mitigate the risks near such edges (Figure 5). Application of a tolerance interval is generally not necessary when the edges of failure are not in play at design space boundaries.

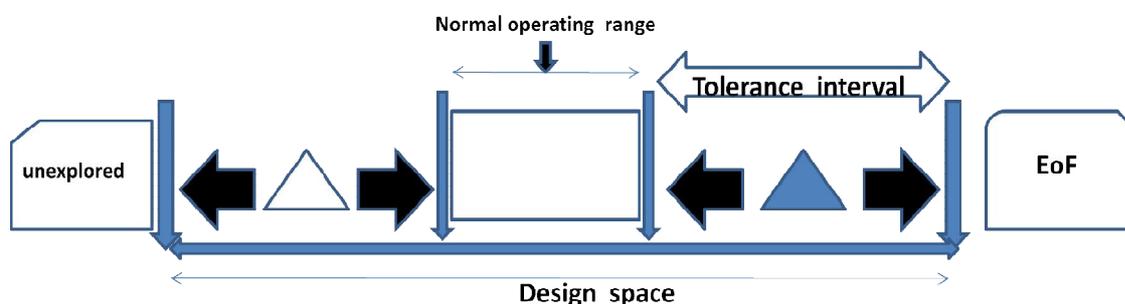


Figure-5 :Design space with an edge of failure (EoF) and use of tolerance interval to mitigate risk.⁽⁶⁾

It can be helpful to determine the edge of failure for process parameters or material attributes, beyond which the relevant quality attributes cannot be met. However, determining the edge of failure or demonstrating failure modes are not essential parts of establishing a design space.

A design space can be described in terms of ranges of material attributes and process parameters, or through more complex mathematical relationships. It is possible to describe a design space as a time dependent function (e.g., temperature and pressure cycle of a lyophilization cycle), or as a combination of variables such as components of a multivariate model.

Example :Robustness of the design

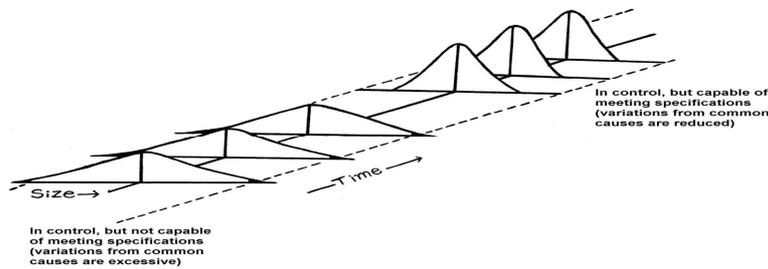


Figure-6: Statistical process capability⁽²⁾⁽⁴⁾

4. Control Strategy:

Definition : Control strategy is defined as “a planned set of controls, derived from current product and process understanding that assures process performance and product quality”^(4&7).

Quality Control Strategy encompasses design Space, process controls and specifications.

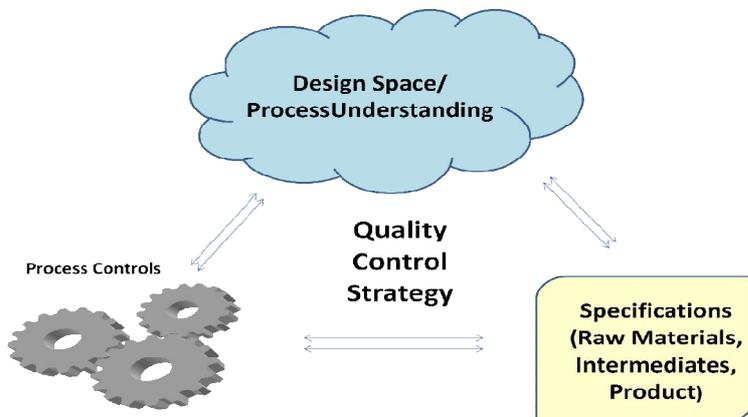


Figure -7: Quality Control Strategy⁽²⁾

Strategy is related to the level of process understanding at a given time, and evolves as manufacturing experience increases. The originally specified measures, controls or models may be modified or even removed, or the need for additional controls may be identified. Other revisions to the Control Strategy may relate to continual improvement, for example the introduction of improved analyser or control technology .

Corrective and preventive actions should be applied and the Control Strategy updated as necessary (including any regulatory actions required) in the light of new product and process knowledge. Implementing PAT in the Control Strategy will require the application of process models (multivariate prediction models) that either predicts COAs or CPPs or a combination of both. These models may require frequent updates, depending on the maturity of the model (e.g., the amount).⁽¹³⁾

A control strategy is what a generic sponsor uses to ensure consistent quality as they scale up their process from the exhibit batch presented in the ANDA to commercial production. Every process has a control strategy right now.^(4&20) Manufacturer are also not permitted to make changes to the operating parameters (a large number of UPPs) specified in the batch record or other process changes without filing supplements with the FDA.⁽²⁰⁾

The control strategy may be further refined based on additional experience gained during the commercial lifecycle of the product. However, any post-approval changes should be reported to the agency in accordance with CFR 314.70 and should follow steps as outlined by guidances used for scale-up and post-approval change.⁽⁷⁾ A control strategy can include different elements. For example, one element of the control strategy could rely on end-product testing, whereas another could depend on real-time release testing. The rationale for using these alternative approaches should be described in the submission.⁽²¹⁾

5. Product life cycle:

In the QbD paradigm, process changes within the design space will not require review or approval ^(7&20). Therefore, process improvements during the product lifecycle with regard to process consistency and throughput could take place with fewer post approval submissions.⁽⁷⁾ 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 ⁽²⁰⁾.

Conclusions:

Quality by design is an essential part of the modern approach to pharmaceutical quality. This paper clarifies the use of QbD including:

1. Emphasis on the importance of the Target Product Quality Profile in articulating a quantitative performance target for QbD.
2. Identification of critical material attributes that provide a mechanistic link of the product quality to the manufacturing process.
3. The role of the control strategy as the mechanism for incremental implementation of QbD elements into practice.
4. An efficient path to a design space through the identification of non-interacting process variables and their exclusion from formal experimental designs.

REFERENCE:

1. PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, September 2004, <http://www.fda.gov/cder/guidance/6419fnl.pdf>.
2. Quality by Design (QbD) - Principles " ,29th jan,2013, Saurashtra University, Rajkot, By Dr C. V. S. Subrahmanyam ,Principal, GokarajuRangaraju College of Pharmacy, Hyderabad
3. Innovation and continuous improvement in pharmaceutical manufacturing pharmaceutical CGMPs for the 21st Century, U.S. Food and Drug Administration, 2004 September, Available from: [URL:http://www.fda.gov/cder/gmp/gmp2004/manufSciWP.pdf](http://www.fda.gov/cder/gmp/gmp2004/manufSciWP.pdf).
4. Food and Drug Administration, Final report on pharmaceutical cGMP for the 21st century A risk based approach, <http://www.fda.gov.com/cder/gmp/gmp2004/GMP>
5. U.S. Department of Health and Human Services Food and Drug Administration (2004) Pharmaceutical GMP for the 21st Century A Risk-Based Approach: Second Progress Report and Implementation Plan.
6. <http://www.ceruleanllc.com/resources/published-articles-case-studies/#QbD>
7. US Food and Drug Administration, Guidance for industry, PAT – A Framework of innovative pharmaceutical Manufacturing and Quality Assurance , Pharmaceutical cGMP, Rockville, MD, 2004 – sept.1-21

8. "FDA's Quality Initiatives –An Updat" , October 24,2006, 10th APIC/CEFIC, Warsaw, Poland, by Moheb M. Nasr, Ph.D. CDER, FDA , MOHEB.NASR@FDA.HHS.GOV
9. "Implementing Quality by Design" , 24 sep, 2007,Helen N. Winkle, Director, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration
10. Quality by Design Approaches to Analytical Methods FDA Perspective, October 25, 2011, by Yubing Tang, Ph.D. FDA/CDER/ONDQAAAPS, Washington DC
11. R. Somma, " Development Knowledge Can Increase Manufacturing Capacity and Faciliate Quality by Design" J. Pharm. Innov. 2, 87-92 (2007)
12. Risk management - Vocabulary - Guidelines for use in standards, July 2002, pg no. 28.
13. Food and Drug Administration: Final report on pharmaceutical cGMPs for the 21st century- A risk-based approach: [http:// www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004. htm](http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm)
14. Lawrence X, Raw A, Lionberger R, Rajagopalan R, Lee L, Holcombe F, Patel R, Fang F, Sayeed V, Schwartz P, Adams P, and Buehler G. U.S. FDA question-based review for generic A new pharmaceutical assessment system. J. Generic Med 2007; 4: 239-248
15. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER),Guidance for Industry , Q9 Quality Risk Management, <http://www.fda.gov/cder/guidance/index.html>
16. Pharmaceutical cGMPs for the 21 Century – A Risk-Based Approach. FDA (CDER), September 2004; <http://www.fda.gov/Drugs/default.htm>.
17. Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2, Second updated edition. Good manufacturing practices and inspection. Geneva, World Health Organization, 2007; Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. World Health Organization, 2011 (CD-ROM) (<http://apps.who.int/medicinedocs/en/q/>).
- 18.** Juran Jm. Juran on quality by design The new steps for planing quality into goods and services newyork free press 1992 p.no-1-2
19. US Food and Drug Adminisration, Guidance for industry, Q10 Quality System approach to pharmaceutical c GMP regulation, , Rockwille, MD, 2006

20. International Conference on Harmonization(ICH) of Technical Requirements for Registration of Pharmaceuticals for HumanUse, TopicQ9: Quality Risk Management, ICH,Geneva,Switzerland, 2005.
21. International Conference on Harmonization(ICH) of Technical Requirements for Registration of Pharmaceuticals for HumanUse, TopicQ2 (R1), :Validation of Analytical Procedures:Text and methodology, ICH, Geneva, Switzerland, 2005.
22. ICH Q9 – Quality Risk Management, Step 4, November 2005, <http://www.ich.org/cache/compo/276-254-1.html>.
23. <http://www.pharmaqbd.com/QbDViewpoint>.
24. <http://www.ich.org> Q8,Q9,Q10 guideline. , Implementation of Quality by Design in pharmaceutical development, Peter watmough, gsk
25. Juran Jm. Juran on quality by design The new steps for planing quality into goods and services newyork free press 1992 p.no-1-2.
26. US. Department of Health and Human Services Food and Drug Administration (2007) PharmaceuticalQualityforthe21st Century: A Risk-Based Approach. <http://www.fda.gov/oc/cgmp/report0507.html>.
27. Rathore AS and Devine, R.(2008) PDA workshop on quality by design for biopharmaceuticals: concepts and implementation,May21-22,2007,
28. Bethesda, Maryland. PDAJ.Pharm.Sci.Technol.,62 (5),380-390.
29. National Institute for Pharmaceutical Technology and Education. Strategic roadmap for research and education. <http://www.nipte.org>; 2006.
30. R. Lionberger et al., "Quality by Design: Concepts for ANDAs," *The AAPS Journal*. 10(2), 268–276 (2008).
31. L. X. Yu. "Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control," *Pharm. Res.* 25(4), 781–791 (2008).
32. Snee, Ronald D,'Quality by Design; Four years and three mynth later' Pharmaceutical processing, <http://www.pharmapro.com>
33. P.J.VonDochren, R. st John Forbes and C.D.Shively, *Pharm Tech.* 6, 139, (1982)