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REVIEW ON QUALITY BY DESIGN (QbD)

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ABSTRACT

Quality by design (QbD) is a new approach to the product development which offers important business benefits throughout the product life cycle. Now-a-days, QbD becomes an essential part in the pharmaceutical quality control process. ICH guidelines Q8 (pharmaceutical development), Q9 (quality risk management) and Q10 (quality systems) forms the basis of QbD. QbD defines the quality target product profile (QTPP), critical quality attributes (CQA), risk assessment and life cycle management to design and develops the formulation and process. The aim of this paper is to describe how QbD can be used to ensure the smooth manufacturing and quality of pharmaceutical products.

Keywords: QbD, ICH guidelines, Pharmaceutical, Quality control, Manufacturing, Design space, QTPP, AQbD.

INTRODUCTION

The word quality was originated from the Latin word '*Qualitus*' which means general excellence or distinctive feature. The simplest definition of quality is fitness for intended use. Quality is the suitability of either drug substance or a drug product for its intended use. This term includes some attributes such as the identity, strength and purity. A drug product that is free from contamination and defects which delivers the labeled therapeutic, pharmacokinetic benefits and reproducibility has high quality. Performance, reliability and durability are the dimensions of quality. Planned quality incorporated in to the product is quality by design (QbD). The term quality by design (QbD) was first proposed by Dr. Joseph M. Juran, and it was applied in the automotive industry. Quality by design (QbD) in pharmaceutical sciences was proposed by Food and Drug Administration (FDA)

and the International Conference on Harmonization (ICH). The basic concept of quality by design is that 'the quality is not to be tested into the product, but it should be built into it [1].

Definition of Quality by Design (QbD)

As per ICH Q8 (R1) guideline: QbD 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[1,2].

As per FDA PAT guidelines: QbD is a system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of new and in-process materials and process will impact on the quality of the product safety."

History of QbD

A concept of QbD was founded by well-known quality expert Joseph M. Juran. During 1986, W. Edwards Deming (in out of crisis), also interestingly explained the concept of quality by design with the example of disease. In 2002 the FDA announced a new initiative (cGMP for the 21stcentury: A risk based approach). This initiative intended to modernize the FDA's regulation of pharmaceutical quality and establish a new regulatory framework focused on QbD, risk management and quality systems. QbD requires an understanding of how product and process variables influence product quality. In addition to this new concept being considered by FDA in its cGMP initiative, two important guidance documents were published as a part of international conference on harmonization (ICH) guidelines: Q8 pharmaceutical development and Q9 quality risk management[3].

Objectives of QbD [3]

The main objective of QbD is to achieve the quality products. Other objectives are:

- To achieve positive performance testing.
- To ensure combination of product and process knowledge gained during development.

Foundation of QbD

ICH guideline Q8 for pharmaceutical development, Q9 for Quality Risk Management and Q10 for Quality systems are foundation of QbD (Fig. 1).

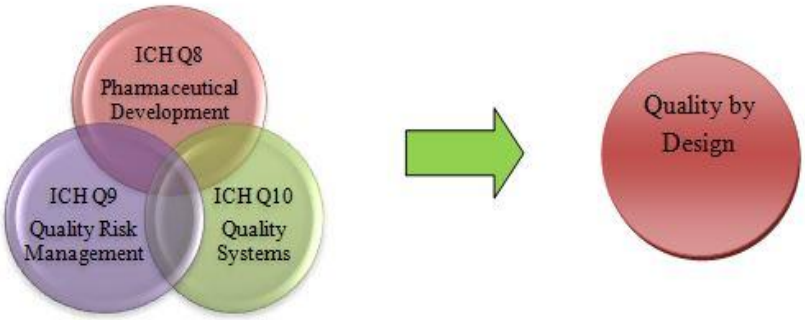

Fig. 1: Foundation of QbD

Advantages of QbD [123]

There are many advantages of QbD as enlisted below:

- It gives higher level of assurance of the quality of the product
- It is cost saving and efficient for industry
- It minimizes or eliminates the potential compliance actions
- It provides opportunities for continual improvement
- It facilitates innovation
- It enhances opportunities for first cycle approval
- It increases process capability and reduce product variability and defects
- It eliminates batch failures
- It empowers technical staff
- It provides better understanding of the process
- It ensures better design of product with fewer problems

The advantages of QbD approach over conventional approach are depicted in Table 1.

Table 1: Comparison between conventional approach and QbD approach

Conventional process	QbD manufacturing process
Variable starting material	Variable starting material
Fixed manufacturing process	Controlled manufacturing process
Variable end product	Consistent end product

Fundamental aspects of QbD [4]

This approach demands a full knowledge of how a product's formulation development and process will impact on the quality of the product (Fig. 2). QbD implies understanding the sources of variability and their impact on the final product and then controlling this variability. The quality of the product is determined by its performance. If QbD is followed carefully, then the need of final product testing is reduced, or even eliminated.

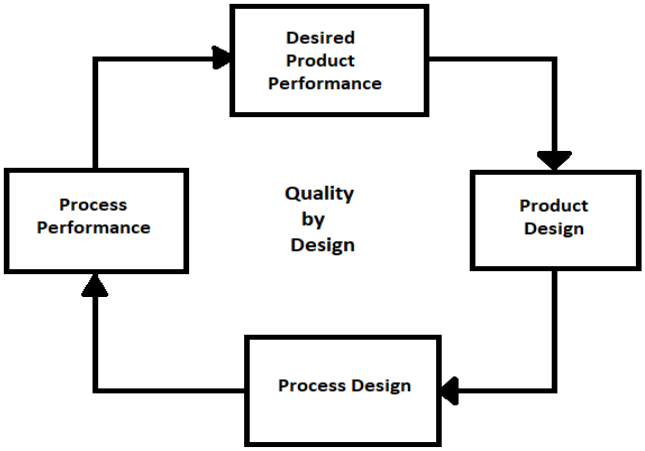

Fig. 2: Fundamental aspects of QbD

Steps involved in QbD / Elements of QbD [5]

1. Clinical development
   - Preclinical study
   - Nonclinical study
   - Clinical study
   - Scale up
   - Submission for market approval
2. Manufacturing
   - Design Space
   - Process Analytical Technology
   - Real Time Quality Control
3. Control Strategy
   - Risk based decision
   - Continuous improvement

- Product performance

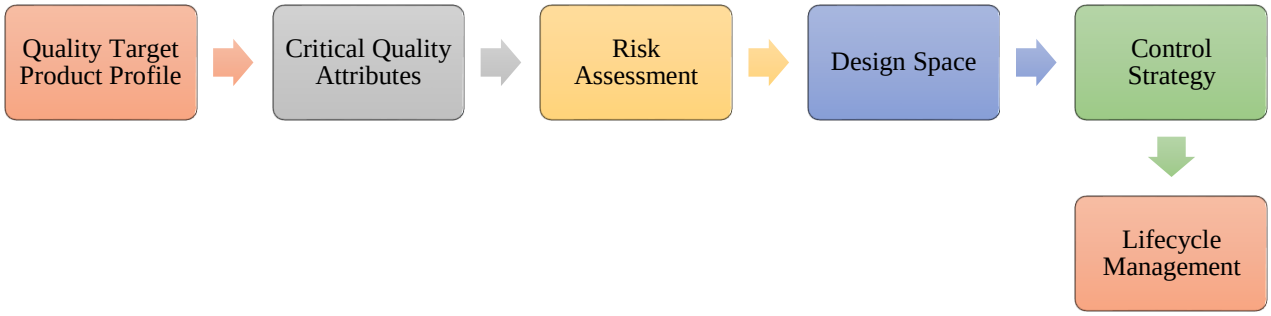

Fig. 3: Elements of QbD

Seven steps of QbD start up plan are as follows:

1. Hire an independent Quality by Design expert
2. Audit your organization and process with the expert conducting a gap analysis
3. Hold a basic Quality by Design workshop with all your personnel
4. Review the expert's report and recommendation
5. Draft an implementation plan, timelines and estimated costs
6. Assign the resources (or contract out
7. Retain the independent expert as your "Project Assurance advisor"

Important attributes about QbD [6]

1. Quality Target Product Profile (QTPP):

The quality target product profile forms the basis of design for the development of the product. It mainly focuses on the safety and efficacy.

Considerations for the quality target product profile could include:

- Intended use in clinical setting, route of administration, dosage forms, livery systems.
- Dosage strength(s)
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance)

- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product

Benefits of QTPP are as follows:

- Identifies risks and best approaches to manage.
- Uses tools/enablers in an optimized fashion (such as integration of QbD and biopharmaceutics)
- Generates and enables knowledge sharing
- An integrative learning, life-cycle process for optimizing decision making and the therapeutic outcomes for the patients benefit
- A drug product designed, developed and manufactured according to Quality Target Product Profile with specification (such as dissolution / release acceptance criteria) consistent with the desired *in vivo* performance of the product

2. Critical Quality Attributes (CQAs):

A Critical Quality Attribute (CQA) is a physical, chemical, biological or microbiological property that should be within an appropriate limit, range or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product.

CQAs of solid oral dosage forms are typically those aspects affecting:

- Product purity, strength,
- Drug release and stability.

CQAs for other delivery systems can additionally include more product specific aspects such as:

- Aerodynamic properties for inhalational products,
- Sterility for parentrals,
- Adhesion properties for transdermal patches.

CQAs for drug substances, raw materials and intermediates include:

- Particle size distribution
- Bulk density

3. Risk Assessment:

Risk Assessment is a valuable science-based process used in quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs. Risk assessment is typically performed early in the pharmaceutical development process and it repeated as more information becomes available and greater knowledge is obtained. They can

overcome by once the significant parameters are identified, they can be further studied to achieve a higher level of process understanding. e.g., through a combination of design of experiments, mathematical models or studies that leads to mechanistic understanding.

Risk Assessment Tools are:

- Failure Mode Effect Analysis (FMEA)
- Failure Mode Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operatability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)

4. Design Space:

The relationship between the process inputs (material attributes and process parameters) and Critical Quality Attributes can be described in the Design Space (Fig. 4). Working within a 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.

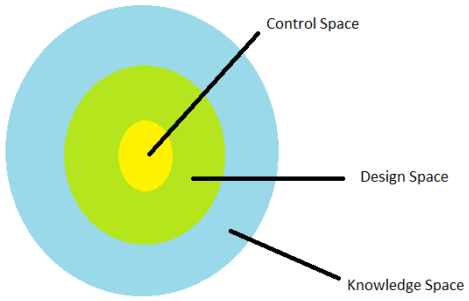

Fig. 4: Design Space

5. Control Strategy:

A control strategy can include:

- Control of input material attributes based on an understanding of their impact on processability or product quality. E.g., drug substance, excipients, primary packaging materials etc.
- Product specification(s)

- Controls for unit operations that have an impact on downstream processing or product quality. e.g., the impact of drying on degradation, particle size distribution of the granulate on the dissolution
- In-process or real-time release testing instead of end-product testing. E.g., measurement and control of CQAs during processing
- A monitoring program. e.g., full product testing at regular intervals for verifying multivariate prediction models.

6. 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.

Barriers to QbD [7]

1. Culture challenges:
   - Move from prescriptive approach
   - More sharing of scientific information
2. Business challenges:
   - Business justification
   - Management support
   - Budgeting silos across business units
3. Implementation challenges:
   - Collaboration between functions
   - Experience with new concepts
   - Workload and resource limitations

Applications of QbD [8]

1. Pharmaceutical Development:

   To design a quality product and a manufacturing process to consistently deliver the intended performance of the product
2. QbD in CMC Review Process:

- Science-based assessment
- Restructured organization and reorganized staff –premarket staff and post-market
- CMC Pilot

- A number of applications submitted
- Lessons learned
- Evaluation of information
- Implementation of PMP

3. Office of New Drug Quality Assessment (ONDQA):

- Science-based assessment
- Restructured organization and reorganized staff –premarket staff and post market
- CMC Pilot
- A number of applications submitted
- Lessons learned
- Evaluation of information
- Implementation of PMP

4. Office of Generic Drugs (OGD):

- QbD contains the important scientific and regulatory review questions
- Evaluate whether a product is of high quality
- Determine the level of risk associated with the manufacture and design of this product
- 416 applications received using QbD by June 2007
- Successful in ensuring that questions address issuesregarding QbD

5. Office of Biotechnology Products:

- Have more complex products
- Already doing some aspects of QbD
- In process of preparing to accept applications using QbD
- Beginning a pilot for biotech products for QbD –usingmainly comparability protocols
- Also implementing Q8, Q9 and Q10

Analytical Quality by Design (AQbD) [9]

Quality by design finds great application in analytical method development, the aim of analytical QbD is (AQbD) is to develop a robust method which is applicable throughout the lifecycle of the drug product and on similar products containing the same active ingredient. Analytical QbD provides flexibility in the analysis of API, drug impurities and biological metabolites. The process of AQbD includes

- Defining the objectives of method development, laying emphasis on product and process understanding and establishing an analytical target profile (ATP).
- Performing experimental design which consists of a selection of analytical technique, obtaining method understanding and performance optimization and designing MODR.
- Finally, risk assessment and method verification are performed to prove that method is applicable throughout the product lifecycle with robustness and ruggedness.

Analytical Target Profile (ATP)

Analytical target profile is parallel to QTPP, defining the goal of the analytical method development process. The Pharmaceutical Research and Manufacturers of America (PhRMA) and European Federation of Pharmaceutical Industries and Associations (EFPIA) define ATP as "A statement that defines the method's purpose which is used to drive method selection, design and development activities." ATP consists of identifying target analytes and selecting the suitable analytical technique for carrying out process.

Method Operable Design Region (MODR)

MODR is the analog of "design space" in analytical QbD. It describes the operating range for critical input variables to achieve the ATP. Working in MODR provides flexibility in changing the method input variables without any post-approval changes.

Process Analytical Technology (PAT) [10,11]

A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes for raw and in-process materials and process with the goal of ensuring final product quality.

- Less failures, less reworks, less recalls
- Flexibility with respect to scale and equipment
- Better/ faster quality systems

Table 2: PAT in Tablet manufacturing

Stage	Technique	Measurement
Dispensing	NIR/ Raman	Identification of raw materials
Wet granulation	NIR	Moisture distribution
Drying	NIR	Moisture content
Blending	NIR	Blend uniformity
Compression	NIR	Content uniformity

Benefits of implementing QbD in FDA [12,13,14]

- Enhances scientific foundation for review
- Provides for better coordination across review, compliance and inspection
- Improves information in regulatory submissions
- Provides for better consistency
- Improves quality of review (establishing a QMS forCMC)
- Provides for more flexibility in decision making
- Ensures decisions made on science and not onempirical information
- Involves various disciplines in decision making
- Uses resources to address higher risks

QbD for industry and regulatory bodies:[15,16]

QbD comprises all elements of pharmaceutical development mentioned in the ICH guideline. The following roles are describe for Pharmaceutical industry and regulatory bodies are listed in Table 3.

Table 3: Role of QbD for industry and regulatory bodies

Industry	Regulatory Agency
Development of scientific understanding of critical process and product attributes.	Scientifically based assessment of product and manufacturing process design and development.
Controls and testing are designed and based on limits of scientific understanding at development stage.	Evaluation and approval of product quality specifications in light of established standards. E.g., purity, stability, content uniformity etc.
Utilization of knowledge gained over the product's life cycle for continuous improvement.	Evaluation of post-approval changes based on risk and science.

Conclusion

Quality by design (QbD) is proposed to develop process knowledge and it is based on existing guidance and reference documents. QbD is quality system that builds on past and sets the potential regulatory expectations. QbD becomes important in the area of pharmaceutical processes like drug development, formulations, analytical methods and biopharmaceuticals. The major reason behind adoption of QbD is the regulatory requirements. Pharmaceutical industry requires a regulatory compliance to get their product official for marketing.

References

1. Q9: Quality Risk Management. ICH Harmonized Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2006.
2. Q10: Pharmaceutical Quality System, ICH Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2007.
3. Q8 (R1): Pharmaceutical Development, Revision 1, ICH Harmonized Tripartite Guidelines, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2007.
4. Juran JM. On quality by design The new steps for planning quality into goods and services Newyork free press. 1992: 1-2
5. Callis JB, Illman DL and Kowalski BR. Process analytical chemistry. Analytical Chemistry. 1987; 59: 624A–637A.
6. Food and Drug Administration. Final Report on Pharmaceutical cGMPs for the 21st Century - A Risk Based Approach. http://www.fda.gov/ cder/ gmp/ gmp 2004/ GMP_ final report 2004.htm. 2016.
7. Jain S. Quality by Design (QbD): A Comprensive understanding of implementation and challenges in pharmaceutical development. Int J of Pharm Pharma Sciences.2014;6(1): 29-35.
8. Sangshetti JN, Deshpande M, Arote R, Zaheer Z and Shinde DB. Quality by design approach : Regulatory need. Arab J Chem. 2014; 1-14.
9. Nadpara NP, Thumar RV, Kalola VN and Patel PB. Quality by Design (Qbd): A Complete Review. Int. J. Pharm. Sci. Rev. Res. 2012; 17(2): 20-28.

10. Gawade A, Chemate S and Kuchekar A. Pharmaceutical Quality by Design: A New Approach in Product Development. Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences. 2013; 2(3): 5-12.
11. Khare R. Three Romeos and A Juliet an Early Brush with Design of Experiments. www.isixsigma.com. 2016.
12. Rathore AS and Winkle H. Quality by Design for biopharmaceuticals. Nature Biotechnology. 2009; 27: 26–34.
13. Remy B, Glasser BJ and Khinast JG. The effect of mixer properties and fill level on granular flow in a bladed mixer. AIChE Journal. 2010; 56: 336–353.
14. Rathore AS and Winkle H. Quality by design for biopharmaceuticals, Nat Biotechnol. 2009; 27: 27-34.
15. Purohit PJ and Shah KV. Quality By Design (Qbd): New Parameter For Quality Improvement & Pharmaceutical Drug Development,Pharma Science Monitor. Int J Pharm Sci. 2013; 4: 1-19.
16. Munson J, Gujral B and Stanfield CF, A review of process analytical technology (PAT) in the U.S. pharmaceutical industry. Current Pharmaceutical Analysis. 2006; 4(2): 405-414.