A Modern Approach for Pharmaceutical Quality Products

B.Gowry Snehitha, B.Charu Hasini A.Divya, K.Aaradhana, A.Revathi, Dr.I.V.Ramarao
NRI College of Pharmacy, Agiripalli Via Nunna, Vijayawada

Abstract: Quality by Design is the modern approach for quality of pharmaceuticals. This paper gives idea about the Pharmaceutical Quality by Design (QbD) and describes use of Quality by Design to ensure quality of Pharmaceuticals. The aim of the pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. Quality cannot be tested into products but quality should be built in by design. It includes the Quality target product profile, critical quality attributes and key aspects of Quality by Design. It also gives comparison between product quality by end product testing and product quality by Quality by Design. The foundation of Quality by Design is ICH Guidelines. It is based on the ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for pharmaceutical quality systems. It also gives application of Quality by Design in pharmaceutical development and manufacturing of pharmaceuticals. Also it includes a short view over the application of Various QbD tools like PAT, CAPA and HACCP in Pharmaceutical industry along with their importance in the Quality aspect of Pharmaceutical products. It also tries to cover the major aspects to be concerned while selecting the wide ranges of designs and statistical tools while employing QbD to a Particular aspect of Pharmaceutical Technology.

INTRODUCTION

The goal of pharmaceutical development is to create a high-quality product and its production method to reliably carry out the function of the product. Pharmaceutical development studies and manufacturing experience have given researchers information and expertise that may be used to generate design space, specifications, and production controls with a scientific basis. Quality risk management may be based on data from pharmaceutical development research. The fact that items cannot be checked for quality means that quality must be included into the design from the beginning.A more methodical approach to development, also known as quality by design, may include, among other things, the incorporation of prior knowledge, the results of research using design of experiments, the use of quality risk management, and the use of knowledge management (ICH Q10) over the course of the product's lifecycle. This methodical technique can improve obtaining the intended product quality and aid in the regulators' understanding of a company's business plan.1-5

Although medicine is generally known as a specific good, the pharmaceutical industry's growth is built on production and innovation. The pharmaceutical business has many concerns about the stringent regulations, nevertheless. The present quality by test (QbT) system (Fig. 1a) uses a series of phases, including testing raw materials, creating fixed drug products, and testing finished goods, to guarantee the quality of the final product.

The materials cannot be utilized for production or released into the market unless all FDA requirements or other standards are met. If not, they must be processed again. Due to a lack of understanding of the processes involved and confusion regarding how substance properties affect the intended product profile, the reasons of failure are sometimes not clearly identified.

Fortunately, a fundamental shift from an empirical procedure to a more scientific and risk-based approach in pharmaceutical quality control will occur with the creation of the concept "Quality by Design (QbD)". QbD (Fig. 1b) is a systematic, risk-based, proactive method for developing pharmaceuticals that starts with predetermined goals and places an emphasis on knowledge of the product and process as well as process control grounded in reliable science and high-quality risk management.

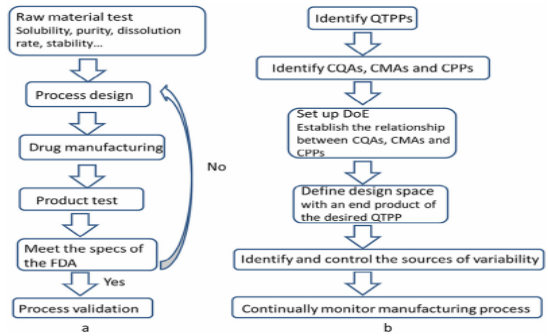


Fig. 1 displays a comparison of the QbT and QbD processes.

DEFINITION:

Quality by Design (QbD) is defined in the ICH Q8 guideline as ‘a systematic approach to development that begins with pre-defined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management‘.6which is in accordance with FDA’s current drug quality system ideology of ‘quality cannot be tested into products; it should be built-in or should be by design.’ ,7

PERKS OF QBD: 1,3,5

1. Batch failures are eliminated
2. Cut back on unnecessary inquiries and diversions
3. Avert issues with legal compliance
4. Technical staff empowerment
5. A system that is effective, adaptable, and agile
6. Improve production efficiency; lower costs, project rejection rates, and waste
7. Create a scientific knowledge basis for all goods
8. Improved communication with business on scientific concerns
9. Ensure accurate information
10. Include risk management
11. Shorten final product testing
12. Fasten the release decision

STEPS CONCERNING QUALITY BY DESIGN PRODUCTS:8,9,10

1.Creation of novelty molecular entity

- Preclinical research
- Non clinical research
- Clinical study
- Scale up
- Submission of regulatory approval

2. Manufacturing

- Design space
- Process analytical technology
- Real time quality control

3. Control strategy

- Risk based decision
- Continuous improvement
- Product performance

STARTUP PLAN FOR QUALITY BY DESIGN:

1. Engage a Quality by Design specialist who is independent.
2. Have the expert doing a gap analysis audit your company and procedure.
3. Organize a fundamental quality by design session with all of your personal.
4. Examine the expert's report and advice.
5. Create an implementation strategy, timelines and expenses.
6. Distribute the resources.
7. Keep the impartial expert as your ‘Project Advisor’ for assurance.

THE FOUNDATION OF QBD: ICH GUIDELINES (ICH Q8, Q9, Q10)11,12.13

ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are foundation of QbD(fig2)

Figure 2: The Foundation of QbD

QBD in relation to ICH:

- Concept alignment
- Design space: The basis for understanding
- Process resiliency
- Quality management
- Design of experiments (DOE)

BACKGROUND OF QUALITY BY DESIGN

The reference document to comprehend the idea of QbD is ICH-Q8: (pharmaceutical development). The definition of QbD is given as follows: "QbD is a systematic way to design a product of predetermined quality and its manufacturing process to continuously and consistently provide intended performance of the finished product.

Based on good science and quality risk management, the information gathered from pharmaceutical development studies and manufacturing experiences was used to logically understand the design of the space's requirements and process controls.

The updated version of ICH-Q8 and its annex are known as ICH-Q8:(R1) and (R2) advice.It covers the tenets of QBD and offers additional explanations of important ideas from the basic guideline.

QbD has been used for many years to produce a variety of goods, much as Design of Experiments, which has been used since the 1920s as factorial designs primarily in agricultural sciences. The approach gained more popularity for industrial uses in the 1950s. FMEA (Failure Modes and Effects Analysis) was created in the 1950s to analyze issues that result from military system failures. A system dependability study's initial step is frequently an FMEA.In 1990, software using the QbD technique continued to advance.

These methods for obtaining better rather than best products led to a greater emphasis on such methods in the pharmaceutical industries. A strategy shift and the inclusion of a more statistical approach in any new development or for the improvement of existing products are the conclusions of the USFDA study on Pharmaceutical cGMP for the 21st century, which lays the foundation for the QbD methodology.(fig3)

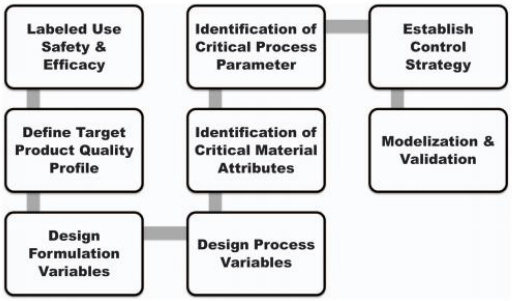


Fig.(3). layout of QbD.

The same terrain yielded additional results in the creation of a new guideline paper from the FDA, namely "PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance."

Although PAT was given more attention, several QbD principles were covered in this advice document. The Common Technical Document (CTD) of ICH-Q8 established the idea of design space in 2005. This Design Space was essentially an approach that focuses on distinguishing between product features and process factors, particularly crucial variables on which the attention should be placed. Risk assessment is the method used to identify the crucial factors. The instruments that may be used to validate risk assessments and verify identified hazards are included in an ICH Q9 recommendation. The following strategy, ICH-Q10, addresses the research and production of pharmaceutical drug substance systems. These rules apply to pharmaceutical drug substances, pharmaceutical drug products, and biological and biotechnological goods.14

The QbD Process's Technical Components:

QbD process consists following technical element as shown in fig 4:15

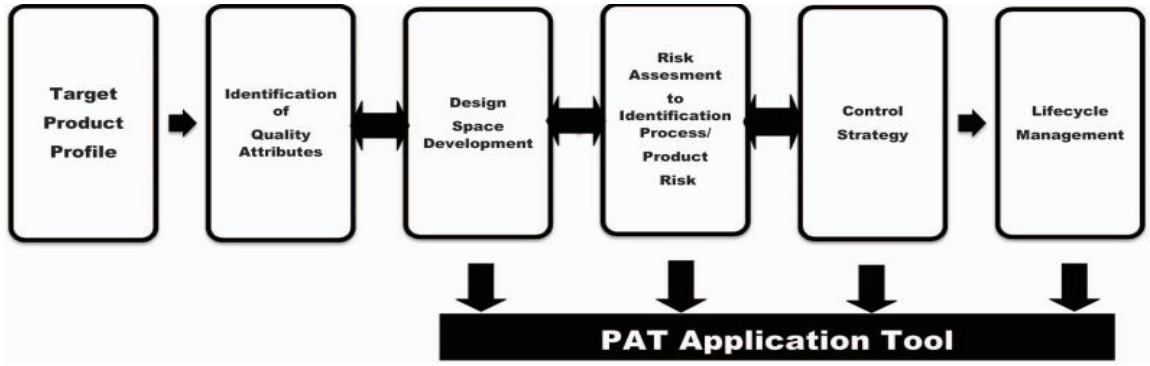
1) Critical Quality Attributes (CQAs) have a significant impact on effectiveness, safety, or repeatable treatment effect, which strongly relates to clinical relevance.

2) Clinically pertinent CQAs that are directly or indirectly related to key process parameters (CPPs).

3) One or more CPPs that manage the clinically relevant CQA made possible by real-time monitoring or PAT.

4) Acceptance requirements, which are determined by dimensional connections between Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs), allowing the operational requirements to be included inside a Design Space.

Fig.(4).Technical elements of QbD



Tools of QBD:

The science behind design and the science of manufacturing make up the two halves of the QbD idea. After comprehending the components of QbD and the procedures for putting them into practice, it's crucial to be knowledgeable about the instruments that are frequently employed in QbD, such as risk assessment, design of experiments (DoE), and progress analytical technology (PAT).

Risk Assessment:

Risk assessment is a methodical procedure for gathering data to support a risk decision that will be made as part of a risk management process. It entails identifying risks, analyzing those risks, and assessing the risks connected to exposure to those risks. The second and third phases of a good risk management process are risk control and risk review. Making decisions to lessen and/or accept risks is a part of risk control. The goal of risk control is to bring the risk down to a manageable level. In order to incorporate fresh information and experience, the output and outcomes of the risk management process should be assessed at the end.Risk communication, or the exchange of knowledge about risk and risk management between the parties (including regulators and industry, industry and the patient, within a company, industry, or regulatory authority, etc.), should take place continuously throughout the entire risk management process. Information may be provided that relates to the existence, kind, form, likelihood, severity, acceptability, control, remedy, detectability, or other characteristics of quality hazards.16

A risk assessment has three parts: risk identification, risk analysis, and risk evaluation.

(1) Risk Identification: The methodical use of information to identify possible causes of damage (hazards) that are related to the risk question or issue description. This information might include past knowledge, theoretical analysis, well-informed opinions, and stakeholder concerns.

(2) Risk Analysis: Which involves calculating the risk posed by the cited dangers.

(3) Risk Evaluation: The process of comparing the predicted risk to predetermined risk standards using a quantitative or qualitative scale to assess the risk.

The following is a non-exhaustive list of the nine popular risk management tools provided by ICH Q9.16

(1) Simple tools for facilitation of risk management (such as the Ishikawa fishbone diagram and flowcharts).

(2) Analysis devoid of errors

(3) Risk classification and filtering

(4) A preliminary study of hazards

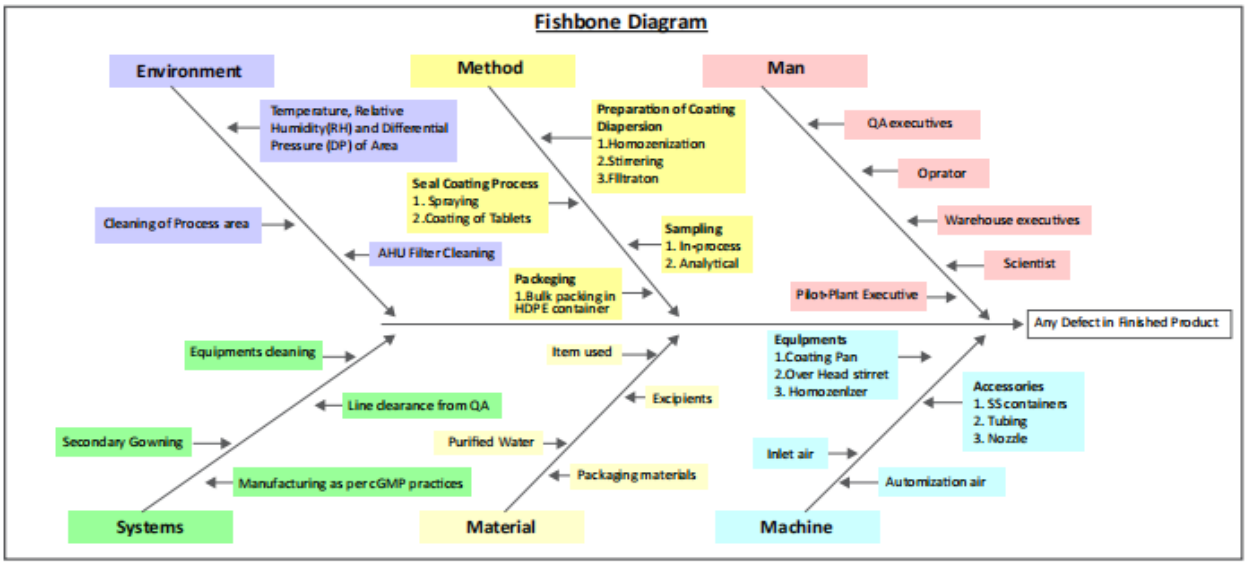
(5) Hazard analysis and crucial safety measures

(6) Failure mode and effects analysis (FMEA)

(7) Failure mode, effects, and criticality analysis (FMECA)

(8) Hazard operability analysis

(9) Supporting statistical tools



Design of Experiment(DoE):

Prior to carrying out the experiment's design, the risk assessment should be put into action. Determine the link between the variables influencing a process and its result using a systematic, organized technique, such as The "Design of Experiments" (DoE). DoE is a fantastic instrument that enables researchers in the pharmaceutical industry to systematically manipulate variables in accordance with a predetermined plan. an excellent layout is founded on accurate product understanding and efficient production process management. Work of DoE studies in addition to studies centered on mechanisms to attain better understanding of products and processes.

DoE is a practical way to establish the connection between a process's inputs and outputs. CMAs, CPPs, and the DesignSpace may all be determined under ideal circumstances with its assistance. Setting up a Design Space using DoE is a good idea for multivariate trials. The Design Space is "the multidimensional combination and interaction of input variables (for example, material attributes) and process parameters that have been demonstrated to provide assurance of quality," according to ICH Q8. 6 According to a study, if the changes are made inside the Design Space, there is no need to submit supplements to the FDA in order to update (for example, extend) the acceptance criteria.

Progress Analytical Technology:

"Tools and systems that utilize real-time measurements, or rapid measurements during processing, of evolving quality and performance attributes of in-process materials to provide information to ensure optimal processing to produce final product that consistently conforms to established quality and performance standards" is how PAT is defined. To make sure that the process stays inside a defined Design Space, PAT is mentioned in ICH Q8.6,16

Numerous tools are provided in the PAT framework to help with understanding scientific, risk-managed pharmaceutical development, production, and quality assurance. They may be divided into four groups based on the PAT recommendations.7

(1) Multivariate tools for design, data acquisition and analysis;

(2) Process analyzers;

(3) Process control tools;

(4) Continuous improvement and knowledge management tools.

APPLICATION

(1) Biopharmaceuticals and biosimilars: The development and production of biopharmaceuticals, such as monoclonal antibodies, vaccines, and biosimilars, is based on QbD principles. In this quickly expanding industry, maintaining constant product performance and quality is essential.

(2) Product Development: QbD concepts are used to identify critical quality attributes (CQAs), critical process parameters (CPPs), and the design space from the very beginning of medication development. This guarantees that quality is considered throughout the product's development.

(3) Process optimization: QbD enables the detection and management of key manufacturing process variables. Pharmaceutical businesses may increase product consistency, lower manufacturing costs, and improve process efficiency by optimizing these variables.

(4) Real-time Monitoring and Control: QbD supports the use of sophisticated process analytical technologies (PAT) for the continuous observation and management of production operations. As a result, if any deviations from the specified quality metrics are found, fast remedial steps are now possible.

(5) Drug Development: QbD concepts are used to identify and comprehend the product's important quality attributes (CQAs) and how they relate to the manufacturing process. This aids in choosing the formulation and process parameters that will result in the production of safer and more potent medicines.

(6) Qualification of Suppliers: Pharmaceutical businesses can use QbD principles to choose and assess suppliers of raw materials and components. This guarantees a reliable supply chain and lowers the possibility of quality problems.

(7) Patient-Centric Approach: QbD ultimately helps patients by making sure that pharmaceuticals are high-quality, safe, and effective. The industry's emphasis on delivering improved healthcare outcomes is consistent with this patient-centered strategy.

(8) Cost savings: QbD can help pharmaceutical manufacturers save money by streamlining operations and reducing the need for in-depth product testing and rework.

CONCLUSION

The rapid increase in interest in QbD and related tools suggests that the methodologies are not passing fads but are solutions to the requirements of contemporary production processes. With DoE, risk assessment, and PAT as its instruments to gain a deeper knowledge of the materials and processes, QbD is a time- and money-efficient design and manufacturing strategy that is made available and practical for the pharmaceutical industry.Drug products of excellent and repeatable quality can be anticipated with its widespread use in pharmaceutical manufacturing. Furthermore, QbD has expanded significantly outside the pharmaceutical (or closely related) industries to become a widely applicable production paradigm. To process a pharmaceutical process in QbD, all ICH guidelines ideas must be understood, whether they are related to product development, quality risk management, or pharmaceutical quality system.

The linkages between all conceivable parameters (the inputs) and all crucial analytical results (the outputs) are investigated during method development. Critical analytical components are determined using a methodology similar to that which is specified for process development in ICH Q8 and Q9. Compared to ICH validation criteria (Q2(R1)), a QbD strategy for analytical techniques that include risk assessment, robustness testing, and ruggedness testing is substantially more stringent. Additionally, it evaluates the method's variability in relation to the specification limitations, which is one of the most crucial method characteristics to check when determining if the method is appropriate for the task at hand.

The strategy outlined here shows that, although offering some value, ICH Q2(R1) has to be significantly updated to take into consideration the QbD risk-based strategies outlined in this article.

Future regulation might potentially be considerably more flexible thanks to this new QbD method. It is possible to register the method performance criteria rather than the actual technique. It is possible to utilize the technique as an illustration of how to meet the necessary method performance requirements. Internal change control processes would apply to any modifications made to this approach.

REFERENCE

1. Woodcock J, The concept of pharmaceutical quality. American Pharmaceutical Review, 7(6), 2004, 10–15.

2. Q9: Quality Risk Management. ICH Harmonized Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.

3. Q10: Pharmaceutical Quality System, ICH Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2007.

4. Lionberger RA, Lee LS, Lee L, Raw A ,Yu LX, Quality by design: Concepts for ANDAs, The AAPS Journal, 10, 2008, 268–276.

5. FDA Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool (Draft Guidance).

6.International Conference on Harmonization (ICH). Guidance for industry: Q8 (R2) pharmaceutical development, ICH harmonised tripartite guideline, step 4. 2009

7. US Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), et al. PAT guidance for industry – A framework for innovative pharmaceutical development, manufacturing and quality assurance. 2004.

8. Callis JB, Illman DL, Kowalski BR, Process analytical chemistry. Analytical Chemistry, 59, 1987, 624A–637A.

9. Yu LX, Pharmaceutical quality by design: Product and process development, understanding, and control. Pharmaceutical Research, 25, 2008, 781–791.

10. Munson J, Gujral B, Stanfield CF, A review of process analytical technology (PAT) in the U.S. pharmaceutical industry. Current Pharmaceutical Analysis, 2, 2006, 405–414

11.Food and Drug Administration, Office of Generic Drugs White Paper on Question-based Review: http://www.fda.gov/cder/ OGD/QbR.htm.

12. Nasr M, FDA's quality initiatives: An update, http://www.gmpcompliance. com/daten/download/FDAs_Quality_Initiative.pdf, 2007.

13. IBM Business Consulting Services, Transforming industrialization: A new paradigm for pharmaceutical development, www-935.ibm.com/services/us/imc/pdf/ge 510– 3997-transforming-industrialization.pdf, 2006.

14. Gracia, T.; Cook, G.; Nosal, R. PQLI key topics-criticality, design space and control strategy. J. Pharm. Innov., **2008**, 3, 60-68.
15. PQRI-FDA Workshop on Setting Drug Specifications for the 21st Century, 1342 Bethesda, MD, March 16-18, **2005**.
16.International Conference on Harmonization (ICH). Guidance for industry: Q9 quality risk management, ICH harmonised tripartite guideline, step 4. 2005.