e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:01/January-2025 Impact Factor- 8.187 www.irjmets.com

QUALITY BY DESIGN: A REVIEW OF CURRENT STATE & FUTURE DIRECTIONS

Dr. D. Rama Brahmareddy*1, Ch. Anuradha*2, N. Sri Lakshmi Deepthi*3

*1Principal, Dept. Of Phytochemistry, Nalanda Institute Of Pharmaceutical Sciences, Guntur, India.

*2Assistant Professor, Dept. Of Pharmaceutical Analysis And Quality Assurance, Nalanda Institute Of Pharmaceutical Sciences, Guntur, India.

*3Student, B.Pharmacy, Nalanda Institute Of Pharmaceutical Sciences, Guntur, India.

ABSTRACT

The newest approach in pharmaceutical production linked to quality is called Quality by Design (QbD). To guarantee that premium-grade pharmaceuticals are produced, Pharmaceutical Quality by Design, or QbD, is discussed in this article. A description of Quality by Design is provided along with a list of its constituent parts. Every unit activity has its own set of quality metrics and characteristics. The use of Quality by Design and its associated measures can yield significant benefits for pharmaceutical goods. The foundation of pharmaceutical R&D is high-quality drugs and the procedures used in their production. A product's quality cannot be easily verified because this paper just summarises the product's quality profile and the most important components of Quality by Design. Quality by design (QbD) and end-product testing are two ways to compare the quality of various goods. Quality by Design is based on the ICH Guidelines. ICH guidelines apply to the development of medications and the application of quality control methods. The research and manufacturing of pharmaceuticals might profit from Quality by Design (QbD). As the product develops and is designed, it is crucial to determine the desired product performance report under these ideas. The TPP, QTPP, and CQA stand for target product profile, quality target product profile, and critical quality characteristics. to identify and regulate sources of changeability and to understand how key material attributes (CAM) and critical process parameters (CPP) of the raw material affect the CQAs. Quality-based drug development (QbD) can provide valuable insights for the design, development, and manufacturing of pharmaceutical products. The present overview discusses the historical context, fundamentals of the QbD methodology, and regulatory requirements. The method's aim, the experiment's design, and the risk assessment are all explained in depth for the QbD aspects. The ICH Guidelines provide the basis of Quality by Design. The ICH Guidelines Q8, Q9, and Q10 for pharmaceutical quality systems, quality risk management, and pharmaceutical development, respectively, serve as its foundation. It also provides information on applying Quality by Design to the creation and production of medicine.[1]

Keywords: Quality By Design, Critical Quality Attributes, Pharmaceutical Analysis, Design Of Experiment, Risk Assessment, Regulatory.

I. INTRODUCTION

The concept was developed by M.Juran in the early's 1970, later QbD concept was instigated into the pharmaceutical industry utterly held up in 2004, hence QbD is not a new concept but old one.The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment 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 quality cannot 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. Design space is proposed by the applicant and is subject to regulatory assessment and approval. 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. In all cases, the product should be designed to meet patients'

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:01/January-2025 Impact Factor- 8.187 www.irjmets.com

needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development, or a combination of both. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management (ICH Q10) throughout the lifecycle of the product. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company's strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle.[3]

Figure 1: Quality by design

II. DESIGN

- Product is designed to meet patient needs and performance requirements.
- Process is designed to consistently meet product quality attributes.
- Impact of starting raw materials and process parameters on product quality is understood.
- Critical sources of process variability are identified and controlled.
- The process is continually monitored and updated to allow for consistent quality over time.[3]

Definition [ICH Q 8(R1)]

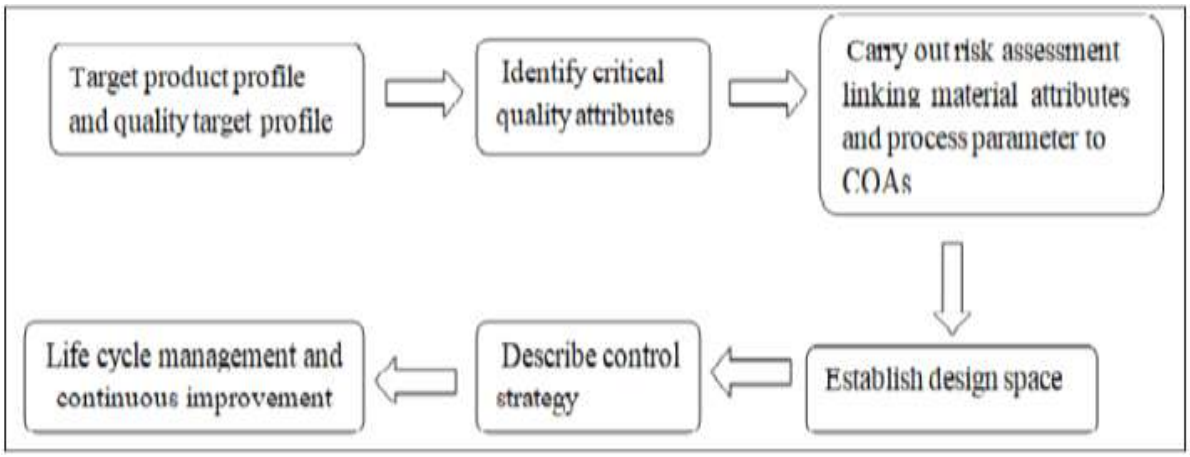
A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Definition [FDA PAT Guidelines, Sept. 2004]

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 processes, with the goal of ensuring final product safety. The concept of "Quality by Design" (QbD) was defined as an approach which covers a better scientific understanding of critical process and product qualities, designing controls and tests based on the scientific limits of understanding during the development phase and using the knowledge obtained during the life-cycle of the product to work on a constant improvement environment. QbD describes a pharmaceutical development approach referring to formulation design and development and manufacturing processes to maintain the prescribed product quality. Guidelines and mathematical models are used to ensure the establishment and use of the knowledge on the subject in an independent and integrated way.[3]

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:01/January-2025 Impact Factor- 8.187 www.irjmets.com

FLOWCHART OF QUALITY BY DESIGN:



6

BENEFITS OF QBD:

- QbD is good Business
- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Organizational learning is an investment in the future
- QbD is good Science
- Better development decisions
- Empowerment of technical staff.[5]

OPPURTUNITIES:

- Efficient, agile, flexible system
- Increase manufacturing efficiency, reduce costs and project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management

Advantages of QbD:

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.[7]

Understanding Pharmaceutical QbD:

QUALITY: : Quality by Design (QbD) is defined in the ICH Q8 guideline as 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.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:01/January-2025 Impact Factor- 8.187 www.irjmets.com

The US Food and Drug Administration initiative to ensure product quality over the whole procedures established in pharmaceutical development of different dosage forms . It is important for all products, including Generics and Biotech.

Purpose and Objectives:

QbD encourages process and product understanding to support innovation and efficiency in product development. Moreover, the application of a QbD approach helps to meet FDA. The benefits of QbD can be translated into an acceleration of product development and a reduction of costs and waste. The quality by Design (QbD) approach to custom 3D printed prostheses can help to ensure that products are designed and manufactured correctly from the beginning without errors.

The FDA publication defined QbD as:

a. Developing a product to meet predefined product quality, safety, and efficacy.

b. Designing a manufacturing process to meet predefined product quality, safety and efficacy. FDA accepted this concept in 2004 and detailed description was given in pharmaceutical cGMPs for the 21st century-

- **A Risk-Based:** The FDA has taken the initiative to guide the pharmaceutical industry on implementing the concept of QbD into its process.
- **FDA's Process Validation:** Guidance in Jan 2011 is for companies to continue benefiting from knowledge gained and continually improve throughout the process lifecycle by making adaptations to assure root causes of manufacturing problems are addressed.

International Conference on Harmonization (ICH): Relevant documents from the international conference on harmonization of the technical requirement for registration of pharmaceuticals for human use. (ICH). US FDA / EMA refer to ICH guidelines Q8, Q9, Q10, Q11 & Q12 for QbD implementation.

- Pharmaceutical Development Q8 (R2).
- Quality Risk Management Q9.
- Pharmaceutical Quality System Q10.

ICH Q8: In the previous decade, the US FDA announced a new pharmaceutical regulatory concept, quality by design (QbD), which has challenged the pharmaceutical industry to design the quality of the final product instead of testing the product. The ICH guideline Q8 definition for 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.

Components of Drug Product Given by ICH Q8:

1. **Drug Substances:** The physicochemical and biological properties of the drug substances that can influence the performance of the drug product and its manufacturability". Example of physicochemical and biological properties includes:

- Solubility.
- Water content.
- Particle size.
- Excipients.

The compatibility of the drug substances with excipients should be evaluated. For products that contain more than one drug substance, the compatibility of the drug substances with each other should also be evaluated.

2. **Formulation Development:** The formulation's development includes identifying those attributes that are critical to the quality of the drug product and highlighting the formulation design's evolution from the initial concept up to the final design. Comparative in-vitro studies e.g., Dissolution (or) in-vivo studies, e.g., BE, link clinical formulations to the proposed commercial formulation.
3. **Container and Closure System:**

- The choice of materials for primary packaging and secondary packaging should be justified.
- A possible interaction between product and container or label should be considered.

ICH Q9: Provides general guidance and references for some of the primary tools used in Risk assessment. Examples are provided for industry and regulators to evaluate the risk to quality based on scientific knowledge and risk to patient.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:01/January-2025 Impact Factor- 8.187 www.irjmets.com

Quality risk management, a part of an effective quality system, helps in identifying the probability of occurrence and severity of the risk. It provides a non-exhaustive list of common risk management tools as follow:

Basic risk management facilitation methods (Ishikawa fishbone diagram, flowchart, check sheets, etc.

- Fault tree analysis.
- Risk ranking and filtering.
- Preliminary hazard analysis.
- Hazard analysis and critical control points.
- Failure mode and effects analysis.

ICH Q10: Pharmaceutical Quality Systems, indicate on an abstract level how Quality by Design acts to ensure drug product quality. Especially for ANDA sponsors, who were not actively involved in the ICH processes .These guideline applies in the process that help in design, development and preparation of drug substances such as API and drug products which includes biotechnology and biological products, throughout the lifecycle of product.[6]

Utilising QbD in the Development of Analytical Methods:

The pharmaceutical industry is embracing QbD because it enables the development of robust, sturdy, and resilient methods that support ICH principles. This methodology enables ongoing technique improvement. Chromatographic methods such as HPLC are used for impurity determination in pharmaceuticals, method development, and stability research. Karl Fisher titration used to calculate the moisture content. Regarding biopharmaceutical procedures. Disintegration investigations. Hyphenated methodology such as LC-MS. sophisticated methods such as capillary electrophoresis, mass spectroscopy and UHPLC. Examining the genotoxic contamination.

STEPS INVOLVED IN QUALITY BY DESIGN PRODUCTS:

1. Development of new molecular entity
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.

Quality Control in Seven Stages using a Design Start up Strategy

1. Hire an independent Quality by design expert.
2. Audit your organization and process with the expert conducting a gape analysis.
3. Hold a basic quality by design workshop with all your personal.
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. (nishendu)

IMPORTANT ELEMENTS OF QBD

a. These elements of a QbD strategy for advancements that are Now that quality, safety, and efficacy can be connected, the TPP can be improved. The standard qualities of the product are determined as a foundation for product planning and development.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:01/January-2025 Impact Factor- 8.187 www.irjmets.com

b. Qualities of Significance Attributes are characteristics of a material that have to fall under certain accepted bounds, ranges, or distributions.

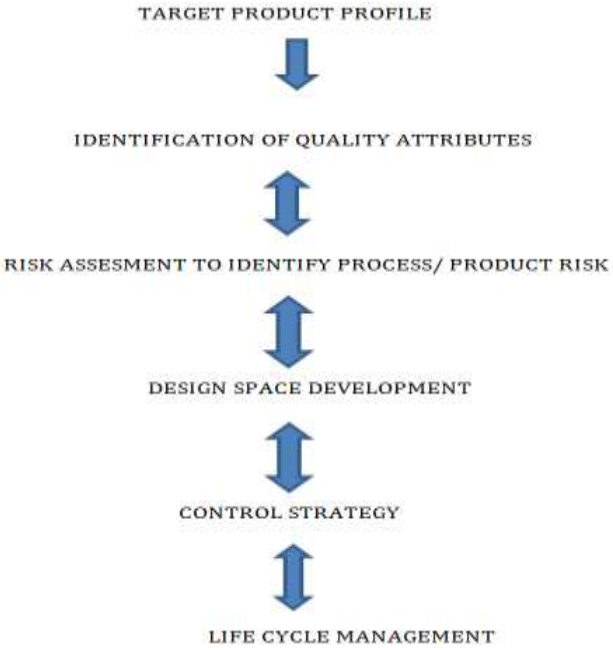
c. In risk assessment, material attributes and CPPs are contrasted with CQAs. Risk assessment instruments such as the FMEA and the bone diagram will be used to calculate the CPPs. The tools that will be utilised for risk management are listed in ICH Q9 20.

d. Utilising experiment style (DOEs) allows for the establishment and representation of a significant stylistic relationship between CQAs and CPPs.

e. The business's long-term strategy when faced with an unexpected situation, it's crucial to quickly identify and solve the issue.

f. Manage product lifetime and continuously enhance quality. The ICH-Q10 standard enhances quality management systems for QbD products throughout their lifespan.

KEY ELEMENTS OF QBD



TARGET PRODUCT PROFILE (TPP):

The TPP outlines the acceptable appearance of a medicinal product for the purposes of medication development and labelling. TPP outlines the goal, target market, administration path, and other crucial components in addition to the product's high-quality design.

TARGET QUALITY PRODUCT PROFILE (TQPP):

In the context of product quality, the word TQPP could be considered a logical extension of the term TPP. The information that cannot be passed down from a single generation to the another must be understood and tracked down using the QTPP. To achieve this, a medication product's desired qualities are outlined, taking into account any potential side effects and safety issues. Quantity, strength, identification, instrumentation closure system, and TQPP are examples of the indefinite-quantity type and purity .An overview of the medication development programme that focuses mostly on safety and efficacy and is presented in terms of labelling ideas.

Description

Clinical Pharmacology

Indications and Usage

Contraindications

Warnings

Precautions

Adverse Reactions

Drug Abuse and Dependence

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:01/January-2025 Impact Factor- 8.187 www.irjmets.com

Over dosage

Dosage and Administration

How Supplied

Animal Pharmacology and/or Animal

Toxicology

Clinical Studies

CRITICAL QUALITY ATTRIBUTES (CQA):

Certificates of conformity, or CQAs, are used in many different contexts to guarantee a product's efficacy, safety, stability, and quality. To ensure that the final product's quality remains within acceptable parameters, it may also be specified, measured, and monitored. Clinical safety and efficacy are examples of quality qualities, together with the parameter border nearing failure. Another aspect of quality is manufacturing. The criticality risk level may increase if the APT manufacturing process's criticality changes.

CRITICAL MATERIAL ATTRIBUTES (CMAs):

When a product cannot meet a QTPP due to a real change in a parameter, it is imperative that the experiment fail. When determining which characteristics are crucial, it's critical to take into account both the degree of modification that one is ready to make and the distinctive qualities of each input material. If the CMAs fall into one or more acceptable ranges, they must satisfy the standards for pharmaceutical substances, excipients, and inprocess materials.

CRITICAL PROCESS PARAMETERS (CPP):

Any measurable input or output of a process step must be managed in order to achieve the appropriate procedure consistency and product quality. Every item in this read would have an approach parameter. This is how it would operate: Prerequisites and in-process parameters that can significantly affect the final product's yield, purity, and attractiveness are checked.

RISK ASSESSMENT:

Speaking of "risk," we mean the possibility as well as the seriousness of harm. A risk-based evaluation of a technique or process may improve its overall quality.

An evaluation of risks is intended to identify the critical components that have an impact on the final product's quality. An evaluation of the risks involved can help to improve communication when dealing with the FDA, trades, R&D/prototype, and multiple production locations. Techniques for evaluating risk include the following 25-26. The ICH guideline Q9 describes a few risk estimation techniques, including:

- Failure Mode Effects Analysis (FMEA).
- Failure Mode, Effects and Criticality Analysis (FMECA).
- Fault Tree Analysis (FTA).
- Hazard Analysis and critical control points (HACCP).
- Hazard Operability Analysis.
- Preliminary Hazard Analysis.
- Risk ranking and filtering.
- Supporting applied mathematics tools.

Design Space:

A design space is defined as the "multidimensional combination and interaction of input variables that have been shown to provide assurance of quality, such as material attributes and process parameters." In a design space, one can account for a single unit of operation, many unit operations, or the entire process. According to FDA rules, one does not need to create a formal design space in order to gain product and process expertise. However, the previously indicated approach can aid in enhancing system understanding and achieving general control. For the new design space, the applicant provides a proposal that has to be authorised by nonsupervisory review. The building of the design space might involve one unit operation, many unit operations, or the whole product formulation process. Although creating a design space is optional according to

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:01/January-2025 Impact Factor- 8.187 www.irjmets.com

FDA rules as product and process knowledge may be obtained without one, a technique like this can help achieve more compassionate product quality and overall system management.

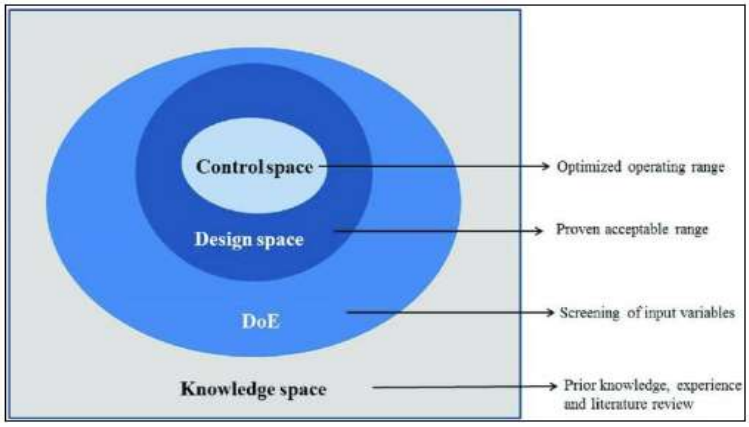


Figure 2: Design space

Utilisation of Design Space:

The Connection between crucial quality qualities and process inputs, including variables and parameters. Used up until the completion of the process or for one or more unit operations. Both before and after MA can be used. By the applicant's proposal. Not seen as a shift in the design space between. It is necessary for the authorities to validate and evaluate.

Control strategy:

Standards for raw materials, system control, and end-product testing are all part of an all-encompassing production plan that yields high-quality goods. Numerous details on the tools and study techniques are available in this system. Because PATs may be adjusted based on your home's decor, they're a terrific tool for this.[1]

TOOLS OF QBD:

Quality risk management (QRM):

FDA defines risk management as a strategic safety program that decreases product risk by using intervention (or) tools. It is a systematic process for the assessment, control, and communication review of risk to the quality of drug across the product life cycle 44. Risk management is the joint responsibility of the quality unit, regulatory affairs, production operations, sales and marketing, and clinical department. Two important principles were highlighted in this document for the use of Quality Risk Management.

1. The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.

2. The level of efforts, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

Design of experiment (DoE):

A structured, organized method for determining the relationship between factors affecting a process and the output of that process is known as" Design of Experiments" (DoE). With the help of DoE, We can define many factors, create designs, construct models, define responses, evaluate the models, interpret results and hence reach a decision. Traditionally we are used to single variant study DoE help to do multivariate analysis e.g., wavelength, flow rate, concentration in case of HPLC and its impact on retention time, resolution, etc. 46. Design of experiment (DoE) is one such structured method that considers the effects of the CMAs and CPPs on the CQAs of the final dosage form. It has gained tremendous attention with the introduction of QbD by the FDA in the formulation development of pharmaceutical products.

PAT (process analytical technology) as an Important Tool of QbD:

PAT is defined as "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

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:01/January-2025 Impact Factor- 8.187 www.irjmets.com

ensure optimal processing to produce a final product that consistently conforms to established quality and performance standards. PAT forms a part of the quality by design (QbD) concept, which provides tools to facilitate the quality.[6]

TRADITIONAL PHARMA IN QBD:

Compared with many industries, the pharmaceutical industry does not routinely utilize enhanced quality systems and state-of-the art equipment. Processes that were quickly developed and submitted to regulatory authorities decades ago remain virtually unchanged. These processes, while delivering acceptable product, also have high reject rates and production costs when compared with other industries. The pharmaceutical industry would benefit from continually modernizing processes using quality concepts and new technology that enhance throughput and provide improved quality and control. There are many factors that have led to this 'traditional' state of pharmaceutical manufacturing. It begins with the focus on drug development, continues to concentrate on the clinical aspects of showing adequate safety and efficacy, and delays most efforts for quality by design until the clinical case has been proven. Although this is financially prudent, it results in a race to register a product with limited understanding and optimization of the manufacturing and testing schemes. Delays in getting products approved result in "lost opportunities" for the firm because there is a limited lifecycle for a pharmaceutical product to return the development investment as patents run out and generic competition drives significant decreases in revenue. The result of launching with a suboptimal process leads manufacturers to reject product batches because of issues that could have been avoided by placing more emphasis on understanding and controlling the processing during the development cycle of the drug. Because quality by design, risk management and quality systems are being introduced as new concepts and ways to do business International Conference on Harmonization (ICH) documents provide global definitions and descriptions of key quality concepts to be adopted. The ICH has tackled the topics of Pharmaceutical Development, Risk Management and Pharmaceutical Quality Systems as Q8, Q9 and Q10. These have been developed and approved through the ICH process. Q8 (Pharmaceutical Development) has just had its first revision approved and focuses on quality by design guidance for pharmaceutical drug products. The establishment of Q8, 9 and 10 provides guidance on the concepts of Pharmaceutical Development, Risk Management and Quality Systems.

Figure 3: QbD Applications

III. CONCLUSION

The capacity to quantify TPPs, continual improvement, and a deeper comprehension of goods and procedures are just a few benefits of the QbD methodology. The design of experiment (DoE) is one such structured method that accounts for the impact of CMAs and CPPs on the CQAs of the final dosage form. QbD has garnered a lot of attention since the FDA applied it to the formulation and development of pharmaceutical items. QbD has emerged as a potentially useful scientific instrument for pharmaceutical sector quality assurance. Getting regulatory permission is the pharmaceutical industry's top priority before releasing any product into the

market. The proper ATP is only one need for QbD; other requirements include risk assessment, tool selection, and timely completion of the necessary amount of labour. For the pharmaceutical sector to guarantee the quality of its products, analytical method development and validation through QbD is crucial. QbD leads to a comprehensive grasp of product development and commercial manufacturing. A time and moneysaving strategy in design and production is called "quality by design." Biotechnological goods including enzymes, vaccines, monoclonal antibodies, etc. are also extensively covered by QbD. Further regulatory flexibility can be facilitated by this new Quality by Design (QbD) methodology. Quality by Design is also no longer limited to the pharmaceutical industry; it is now a widely used production paradigm.

IV. REFERENCES

[1] Ambati Vamsi Krishna , Paradeshi Mounika , G. Vedavathi Sai and Kannedari venkatesh A REVIEW ON QUALITY BY DESIGN APPROACH (QBD) AND IT'S BENEFITS, International Journal of Pharmacognosy, IJP (2024), Vol. 11, Issue8,2394-5583.

[2] Sachin L. Darkunde A REVIEW ON QUALITY BY DESIGN International Journal of Pharmaceutical Chemistry and Analysis, IJPCA (2018), Vol.5, Issue1, 1-6.

[3] Nishendu P. Nadpara, Rakshit V. Thumar, Vidhi N. Kalola, Parula B. Patel QUALITY BY DESIGN (QBD) A COMPLETE REVIEW International Journal of Pharmaceutical Sciences Review and Research IJPSRR (2012),Vol.17,Issue 2, 20-28.

[4] Manu Shree, Chandramouli REVIEW ON QUALITY BY DESIGN APPROCH (QBD) current trends in biotechnology and pharmacy (2021), Vol.15, Issue4, 447-454.

[5] Vemuri Pavan Kumar N. Vishal Gupta A REVIEW ON QUALITY BY DEISGN APPROCH (QBD) FOR PHARAMACEUTICALS International journal of drug development and research (2015), Vol.7, Issue1, 52-60.

[6] P. N. Mallikarjun , Pooja Kumari, S. Manoj Kumar and G. Sowmya AN OVERVIEW ON QUALITY BY DESIGN IN PHARMACEUTICAL PRODUCT DEVELOPMENT International journal of pharmaceutical science and research IJPSR (2022),Vol.13,Issue6,2283-2293.

[7] Gayatri P. Gage, Mithun Rudrapal , Anil G. Jadhav, Laxmikant B. Borse, Atul R. Bendale REVIEW ON QUALITY BY DEISGN (QBD) Asian Journal of Pharmaceutical Education and Research AJPER (2020),Vol.9,Issue2,37-49.