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A REVIEW OF THE QUALITY BY DESIGN IN FORMULATION

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ABSTRACT

This review further clarifies the concept of pharmaceutical quality by design (QbD) and describes its objectives. QbD elements include the following: a quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product; product design and understanding including identification of critical material attributes (CMAs); process design and understanding including identification of critical process parameters (CPPs), linking CMAs and CPPs to CQAs; a control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process; and process capability and continual improvement. QbD tools and studies include prior knowledge, risk assessment, mechanistic models, design of experiments (DoE) and data analysis, and process analytical technology (PAT). As the pharmaceutical industry moves toward the implementation of pharmaceutical QbD, a common terminology, understanding of concepts and expectations are necessary. QbD could be a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and method management supported sound science and quality risk management (ICH Q8 QbD suggests that coming up with and developing formulations and manufacturing processes to make sure predefined product quality.

Product quality is ensured by staple testing, drug substance manufacturing, a fixed drug product manufacturing process, in-process material testing, and end product testing. If they meet the manufacturer's proposed and FDA approved specifications or other standards like USP for drug substance or excipients, they can be used for the manufacturing of the products.

KEYWORD: *Quality, QbD, FDA, Control strategy, Critical quality attributes, Pharmaceutical quality by design, Process understanding, Product understanding.*

INTRODUCTION

Quality by design (QbD) is a concept first developed by the quality pioneer Dr. Joseph M. Juran Dr. Juran believed that quality should be designed into a product, and that most quality crises and problems relate to the way in which a product was designed in the first place. Woodcock defined a high-quality drug product as a product free of contamination and reliably delivering the therapeutic benefit promised in the label to the consumer. The US Food and Drug Administration (FDA) encourages risk-based approaches and the adoption of QbD principles in drug product development, manufacturing, and regulation.

pharmaceutical QbD has evolved with the issuance of ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System) . In addition, the ICH Q1WG on Q8, Q9, and Q10 Questions and Answers; the ICH Q8/Q9/Q10 Points to Consider document; and ICH Q11 (Development and Manufacture of Drug Substance) have been issued, as have the conclusions of FDA-EMA's parallel assessment of Quality-By-Design elements of marketing applications.

Quality

Quality is the degree to which an object or entity (e.g., process, product, or service) satisfies a specified set of attributes or requirements. The quality of something can be determined by comparing a set of inherent characteristics with a set of requirements.

Quality By Design (QbD)

- It is systemic Process for development that start with pre-define objectives and help of the product and process of understanding and process of control and quality risk management.
- Quality by design is an approach that aims to ensure the quality of medicines by employing statistical, analytical and risk-management methodology in the design, development and manufacturing of medicines.

Advantage Of QbD

- Continuous improvement. QbD can ensure a safe and effective drug supply, while also significantly improving the quality of manufacturing performance.
- Better understanding or process.
- Less batch flayer.
- Allow for continuo sally improvement.
- Risk identification

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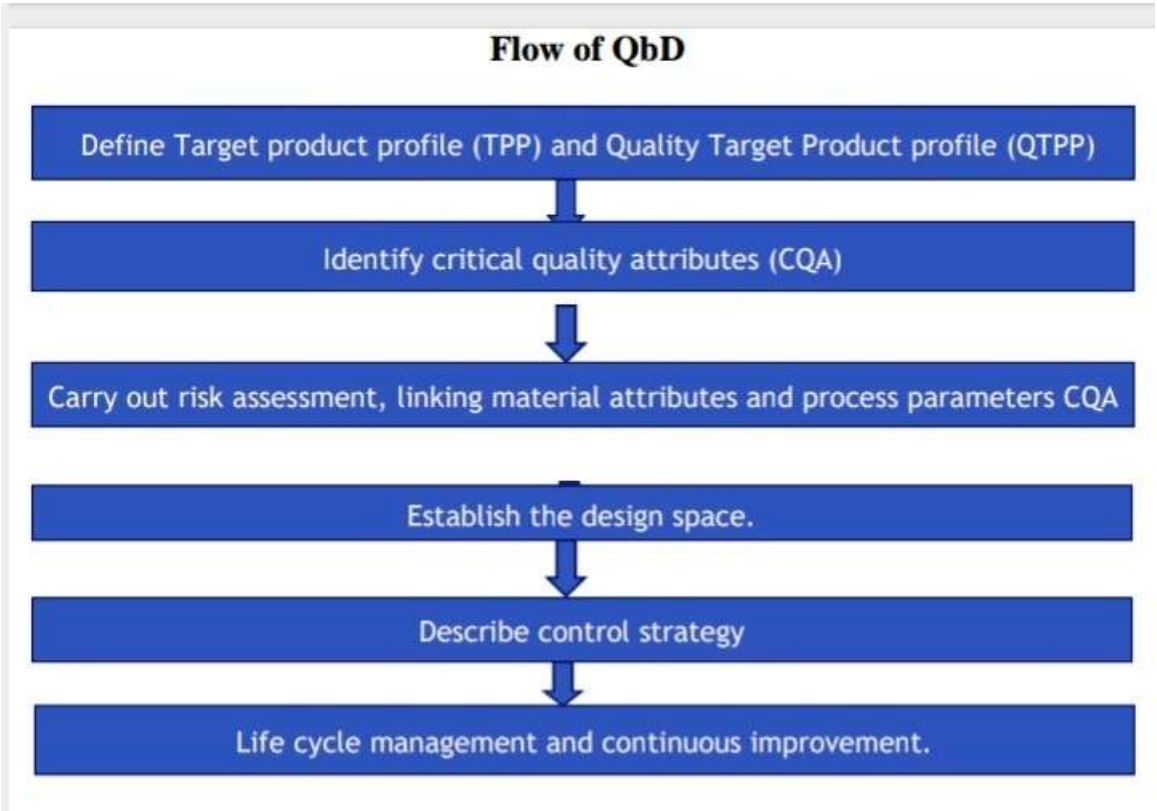
- Provide better consistency.
- Insecure better design of product.

Disadvantage of QbD

- Complex and time consuming.
- Matrix size is too big.
- Contradictory CRs or not easy to solve.

Objectives of QbD

- To achieve meaningful product quality specifications that are based on clinical performance.
- To increase process capability and reduce product variability and defects by enhancing product and process design, understanding, and control.
- To increase product development and manufacturing efficiencies.
- To enhance root cause analysis and post approval change management.
- To understand the effect of raw material and Manufacturing Process.



Overview of QbD

- QbD First develop by Dr. M. Juan.
- QbD descried in ICH Q8,Q9,Q10, guideline in 2006 for pharmaceutical industry.
- Quality by Design is a strategic approach employed in various industries, including pharmaceuticals, manufacturing, and product development, to ensure the consistent delivery of high-quality products.

Element of QbD

- Quality Target Profile Protection (QTPP).
- A quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product.
- Product design and understanding including the identification of critical material attributes (CMAs).
- Process design and understanding including the identification of critical process parameters (CPPs) and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs.
- A control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process.
- Process capability and continual improvement.

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- Design Space.
- Control Spesinge.

Quality Target Profile Perfection For Critical Quality Attributers

QTPP is a summary of quality a drug product that ideally will to be insure the required quality taking in to safety and efficacy of the drug products.

QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. QTPP forms the basis of design for the development of the product.-

- Intended use in a clinical setting, route of administration, dosage form, and delivery system.
- Dosage strength.
- Container closure system.
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (*e.g.*, dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed.
- Drug product quality criteria (*e.g.*, sterility, purity, stability, and drug release) appropriate for the intended marketed product.

Target Product Profile (TPP)

A prospective summary of the quality characteristics of drug product that ideally will be achieved to ensure the desired quality, taking in to account safety & efficacy of drug product."(ICH Q8) Target product profile should includes-

- Dosage form
- Route of administration
- Dosage strength
- Pharmacokinetics
- Stability

The TPP is a patient & labeling centered concepts, because it identifies the desired performance characteristics of the product, related to the patient's need & it is organized according to the key section in the drug labeling.

Critical Quality Attributes (CQAs)

A CQA has been defined as "a physical, chemical, biological or microbiological property or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality. Critical Quality Attributes are generally associated with the drug substance, excipients, intermediates and drug product. The quality attributes of a drug product may include identity, assay, content uniformity, degradation products, residual solvents, drug release, moisture content, microbial limits.

Product Design

ICH Quality Assurance define design of product at the multidimensional combination and interaction of process parameter that have been demonstrate to provide Assurance of quality.

Over the years, QbD's focus has been on the process design, understanding, and control, as discussed in the ICH Q8 guidance It should be emphasized that product design, understanding, and control are equally important. Product design determines whether the product is able to meet patients' needs, which is confirmed with clinical studies. Product design also determines whether the product is able to maintain its performance through its shelf life, which is confirmed with stability studies. This type of product understanding could have prevented some historical stability failures.

Process of Design

A pharmaceutical manufacturing process usually consists of a series of unit operations to produce the desired quality product. A unit operation is a discrete activity that involves physical or chemical changes, such as mixing, milling, granulation, drying, compression, and coating. A process is generally considered well-understood when all critical sources of variability are identified and explained, variability is managed by the process, and product quality attributes can be accurately and reliably predicted.

Benefits Of QbD

- QbD is good science.
- Better development.
- QbD is good Business.
- Empowerment of technical staff.
- Eliminate Batch failures.

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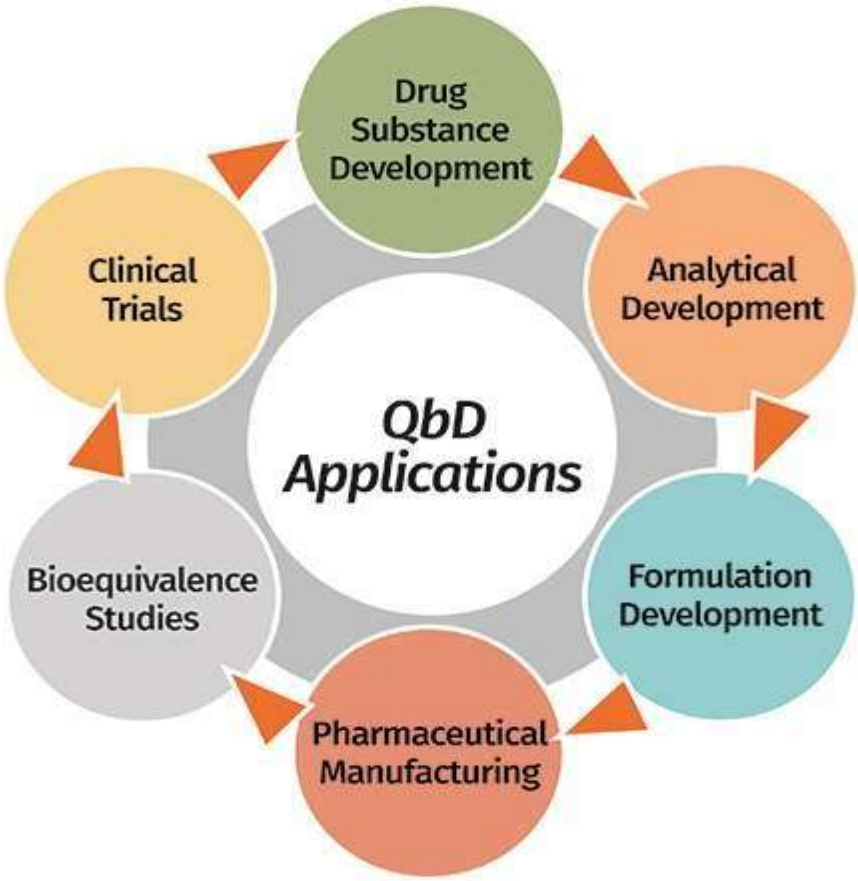
- Minimize deviations and costly investivegation.

.**Opportunities**

- Economical,agile,bersatile system
- Increase producing potency, scale back prices and project rejections and west.
- Build knowledge domain base for all product.
- Higher move with business on science problems.
- Guarantee consistent information.
- Incorporate risk management.

QbD For Application

- QbD Principle ware applied to accelerate Process development to manufacture a vaccine candidate scale.
- Analytical Research development .
- Quality Assurance
- Regulatory affairs.



Pharmaceutical Quality by Design

Quality means fitness for intended use. Pharmaceutical quality refers to product free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer. The Quality of the pharmaceutical product can be evaluated by in vivo or in vitro performance tests. Quality by design assures in vitro product performance and In vitro product performance provides assurance of in vivo product performance. “Hence Quality by design relate to Product Performance”.

QbD Tool

There are Different tool of Quality by Design:-

I. Quality Risk Assessment
II. Design of Experiment (DOE)
III. Process Analytical Technology

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I. **Quality Risk Assessment**
A quality risk assessment is a systematic process of identifying, analyzing, and evaluating the potential hazards and consequences that may affect the quality of a product, service, or process.

II. **Design of Experiment (DoE)**
Design of experiments (DOE) is a systematic, efficient method that enables scientists and engineers to study the relationship between multiple input variables (aka factors) and key output variables (aka responses). It is a structured approach for collecting data and making discoveries.

III. **Process analytical technology**
Process analytical technology (PAT) has been defined by the United States Food Drug Administration (FDA) as a mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of critical process parameters (CPP) which affect the critical quality attributes.

ICH Guideline
ICH- (International Conference on Harmonization)
I- Stand for International means between different Nations.
C- Stand for Configuration tjat means meeting between Difference Country.
H- Stand for Harmonization means Collection of data and propose the draft and stebilisement of data.

Purpose of ICH
- ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective and high quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting high standards.
- To promote public health.
- To promote/prevent unnecessary duplication of Clinical Trial.
- To avoid health of human volumetric to import and export.
- To import and export drugs in all the countries.

ICH Members / ICH Participants
- Current time various regulatory bodies / Countries /portion are member of ICH.
- Ministry of health labor and wayfarer-(MHLW).
- Japan Pharmaceutical Manufacture Associations-(JPMA).
- Food Drug Administration (FDA).
- World Health Organization-(WHO).

ICH Harmonization Process
Step;1- Formal ICH Procedure &New topic for harmonization of ICH
Step;2- Q & A Procedure or classification of exiting guideline
Step;3- Revision Procedure
Step;4- Maintenance procedure
Step;5- Implementation

Overview of QSEM
Q SEM:- (Quality Safety Efficacy Multidiscipliery)
Quality Guidelines:-
Q1A – Q1F Stability
Q2 - analytical validation
Q3A – Q3E Impurities
Q4A- Q4B Pharmacopoeias
Q5A –QSE Quality of Biotechnological Procedures
Q6A- Q6B Specificaturings
Q7 - Good Manufacturing
Q8 - Pharmaceutical development
Q9 - Quality Risk Management
Q10 - pharmaceutical Quality System
Q11 - Development and Manufacture of Drug Substance
Q12 - Lifecycle Management
Q13 - continuous Manufacturing of Drug Substances and Drug products
Q14 - Analytical Procedure Development

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Safety Guidelines:-

S1- Carcinogenicity Studies
S2- Geno-toxicity Studies
S3- Toxico-kinetics and Pharmacokinetics
S4- Toxicity Testing
S5- Reproductive toxicology
S6- Biotechnological Product
S7- pharmacology Studies
S8- Imuno-toxicology Studies
S9- Nonclinical evaluation for anticancer Pharmaceutical
S10- Photo safety Evaluation.

Efficacy Gaudiness

E1&E2- Clinical Safety
E3- Clinical Study Reports
E4- Dose-response Studies
E5- Ethnic Factors
E6- Good Clinical Practice
E7,E8,E9,E10,E11- Clinical Trials
E12- Guidelines for Clinical Evaluation by therapeutic Category
E14- Clinical Evaluation
E15& E16- Pharmacogenomics.

Multidisciplinary Gaudiness'

M1- Med DRA Terminology
M2- Electronic Standards
M3- Non-clinical Safety Studies
M5- Data elements & Standards for Drug dictionaries
M6- Gene Therapy
M7- Genotoxic impurities.

Philosophies of QBD

- Right-first-time batches.
- Safer, higher quality, optimized products.
- Built-in change controls and quality assurance.
- Consistent compliance.
- Decreased oversight and increased flexibility within a proven design space.
- Shorter lead times and getting to market faster.

Tool QBD

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Formulation Design and Development

Formulation design and development involves a combination of various components and optimization of process parameters. Excipients are considered as the vital component of the quality drug product, and it is mandatory to ensure that product development should not result in any incompatibility.

Not all prototype formulations are often evaluated in human subjects, which mean that developing sensitive in vitro dissolution methods is crucial to an efficient development program. FDA's recommended in vitro dissolution method is usually used for internal control .Generic-drug sponsors report using in-house methods for pharmaceutical development (some mentioned using as many as five biorelevant dissolution conditions) to gauge formulations and processes before performing bioequivalence studies. In current practice, pharmaceutical scientists develop a battery of biorelevant dissolution methods to accelerate drug-product development. Further, Biopharmaceutics arrangement is effective guiding formulation development. To establish formulation robustness, sponsors of abbreviated new drug applications (ANDAs) generally evaluate relevant quality attributes of product manufactured at the laboratory scale.

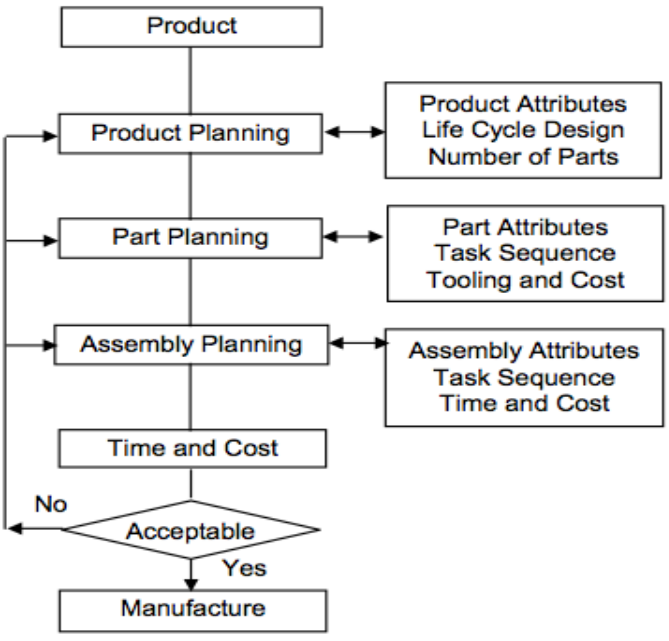
The availability of drug substance may influence the amount of studies and thus , product understanding. QbD should believe the relevance of individual studies instead of the amount of studies because one among the objectives of QbD is to know how the fabric attributes of the drug substance and excipient influence product quality. Formulation design space (pre-approved ranges) would be valuable to industry if appropriate regulatory flexibility is granted. However, the establishment of formulation design space shouldn't delay FDA's approvals. FDA considers the establishment of formulation design space as a post approval activity.

Manufacturing Process Design

Design for Manufacturing (DFM) is the process of designing parts, components or products for ease of manufacturing with an end goal of making a better product at a lower cost. This is done by simplifying, optimizing and refining the product design.

Process development and formulation design can't be separated because a formulation cannot become a product without a prescribed process. Process design is the initial stage of process development, during which an overview of the commercial manufacturing processes is documented, including the intended scales of manufacturing. The outline should include all the factors that need to be considered for the planning of the method , including facility, equipment, material transfer, and manufacturing variables. Other factors to consider during process development are the QTPP and CQAs.

. Depending upon the merchandise being developed, sort of process, and process knowledge the event scientists have, it's going to be necessary to conduct preliminary feasibility studies before completing the process development. The selection of the type of process depends upon the formulation and therefore the properties of the materials. Strictly speaking, process and product design and development can not be separated since a formulation can not become a product without a process. A formulation without a process is, for instance , a pile of powder.



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CONCLUSION

The goals of implementing pharmaceutical QbD are to reduce product variability and defects, thereby enhancing product development and manufacturing efficiencies and post approval change management. It is achieved by designing a robust formulation and manufacturing process and establishing clinically relevant specifications. The key elements of pharmaceutical QbD can include the QTPP, product design and understanding, process design and understanding, and scale up, control strategy, and continual improvement. Prior knowledge, risk assessment, DoE, and PAT are tools to facilitate QbD implementation. Finally, product and process capability is assessed and continually improved post approval during product lifecycle management.

Bilayer tablets have opened new opportunities in the pharmaceutical industry because of their ability to successfully deliver active substances to avoid incompatibilities in solubility, stability, and therapeutic efficacy in a single dosage form. Quality by design is an essential part of the modern approach to pharmaceutical quality. This is a concept that can and is replacing the traditional approach, and is firmly taking roots in the industry

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