

QUALITY BY DESIGN

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Abstract: Quality by way of Design is the cutting-edge strategy for pleasant of pharmaceuticals. This paper offers notion about the Pharmaceutical Quality by using Design (QbD) and describes use of Quality by way of Design to make sure fantastic of Pharmaceuticals. The Quality through Design is described and some of its factors identified. The goal of the pharmaceutical development is to layout a fine product and its manufacturing manner to persistently supply the supposed overall performance of the product. Quality can't be examined into merchandise however nice have to be constructed in through design.

It consists of the Quality goal product profile, fundamental fantastic attributes and key elements of Quality by using Design. It additionally offers assessment between product satisfactory through end product checking out and product pleasant by using Quality by using Design. The basis of Quality with the aid of Design is ICH Guidelines. It is primarily based on the ICH Guidelines Q8 for pharmaceutical development, Q9 for fine danger management, Q10 for pharmaceutical pleasant systems. It additionally gives utility of Quality by way of Design in pharmaceutical improvement and manufacturing of pharmaceuticals.

Keywords: Quality by Design (QbD), Process Analytical Technology (PAT), Quality target product profile, Critical quality attributes.

INTRODUCTION

The purpose of pharmaceutical improvement is to layout a quality product and its manufacturing system to consistently supply the supposed overall performance of the product. The statistics and know-how received from pharmaceutical improvement research and manufacturing experience supply scientific appreciation to guide the institution of the layout space, specifications, and manufacturing controls. Information from pharmaceutical development research can be a groundwork for nice threat management. It is vital to understand that quality cannot be examined into products; i.e., best need to be built in by means of design. (1) in system and manufacturing tactics for the duration of improvement and lifecycle administration ought to be regarded upon as opportunities to achieve additional understanding and similarly support institution of the plan space. Similarly, Inclusion of applicable expertise won from experiments giving surprising consequences can additionally be useful. Design area is proposed by using the applicant and is difficulty to regulatory assessment and approval. Working inside the layout space is now not viewed as a change. Movement out of the design house is viewed to be a trade and would normally provoke a regulatory put up approval alternate process. (2)

In all cases, the product need to be designed to meet patients' desires and the supposed product performance.(3'4) Strategies for product improvement range from business enterprise to company and from product to product.(5) The method can also range and ought to be outlined in the submission. An applicant would possibly pick out both an empirical method or a more systematic method to product development, or a combination of both. (6) greater systematic strategy to development (also described as great by means of design) can include, for example, incorporation of prior knowledge, results of research the usage of format of experiments, use of quality danger management, and use of expertise management (ICH Q10) at some stage in the lifecycle of the product. Such a systematic method can decorate achieving the favored fantastic of the product and assist the regulators to higher apprehend a company's strategy. Product and method grasp can be up to date with the know-how won over the product lifecycle. (7)

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.

Definition

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. (8)

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 (9)

Opportunities

- 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 (10)



FIG NO. 1 QUALITY BY DESIGN

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 (11)

3. Control Strategy

- Risk based decision
- Continuous Improvement
- Product performance (12)

Seven steps of quality by design start up plan

1. Hire an independent Quality by design expert.
2. Audit your organization and process with the expert conducting a gape analysis.
1. Hold a basic quality by design workshop with all your personal.
2. Review the expert’s report and recommendation.
3. Draft an implementation plan, timelines and estimated costs.
4. Assign the resources (or contract out).
5. Retain the independent expert as your “Project Assurance” advisor. (13)

Quality by design (QbD) and well understood product and processes

- All critical sources of variability are identified and explained.
- Variability is controlled by the process.
- Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, environmental and other conditions.
- To gain enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters considering appropriate use of quality risk management principles. (14)

QBD BY PHARMACEUTICALS

Even though the pharmaceutical industry has focus on quality, it has failed to keep up with other industries in terms of manufacturing efficiency and productivity.

Current scenario in the Pharmaceutical Industry:

- Cost of revalidation
- Off-line analysis for in-process - need based
- Product specifications as primary means of control
- Unpredictable Scale-up issues
- Inability to understand failures (15)

Systematic approach to development:

- That begins with predefined objectives
- Emphasizes products and process understanding
- Process control (Figure 1) (16)



Fig. No 2 Process, Quality, Design and PAT

QUALITY TARGET PRODUCT PROFILE

A summary of the drug development program described in terms of labeling concepts and it mainly focus on the safety and efficacy.

- Description
- Clinical Pharmacology

- Indications and Usage
- Contraindications
- Warnings
- Precautions
- Adverse Reactions
- Drug Abuse and Dependence
- Over dosage
- Dosage and Administration
- How Supplied
- Animal Pharmacology and/or Animal Toxicology
- Clinical Studies

A natural extension of Target Product Profile for product quality – Quality characteristics (attributes) that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label guide to establish formulation strategy and keep the formulation effort focused and efficient. (17)

- It facilitates identification of what’s needed/critical for the Patient/consumer in the Quality Target Product Profile (such as Critical Quality Attributes, CQAs).
- 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 iterative, learning, life-cycle process for optimizing decision making and the therapeutic outcomes for the patient 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. (18)

CRITICAL QUALITY ATTRIBUTES

It is necessary to identify the quality attributes that are critical, i.e. those defining purity, potency and surrogate for Bioavailability Criticality etc. It is based on the impact of quality attribute/ parameter on the safety, efficacy & quality (manufacturability) of the product.

- Establish a link between CPP & CQAs: Identification of Attribute or parameters that can be used as a Surrogate for clinical safety & efficacy (important to Patient).
- Manufacturability is also an attribute (important to business) that is critical to quality.
- The level of criticality may differ for an API Manufacturing process relative to a drug product manufacturing process.
- API is one component of a drug product and one step further away from the patient continuum of criticality. Several levels of criticality may be used to describe multiple levels of risk.
- As attribute or parameter boundaries approach edges of failure, the level of critically increased with the risk. (19)

Flow Chart of QbD Process

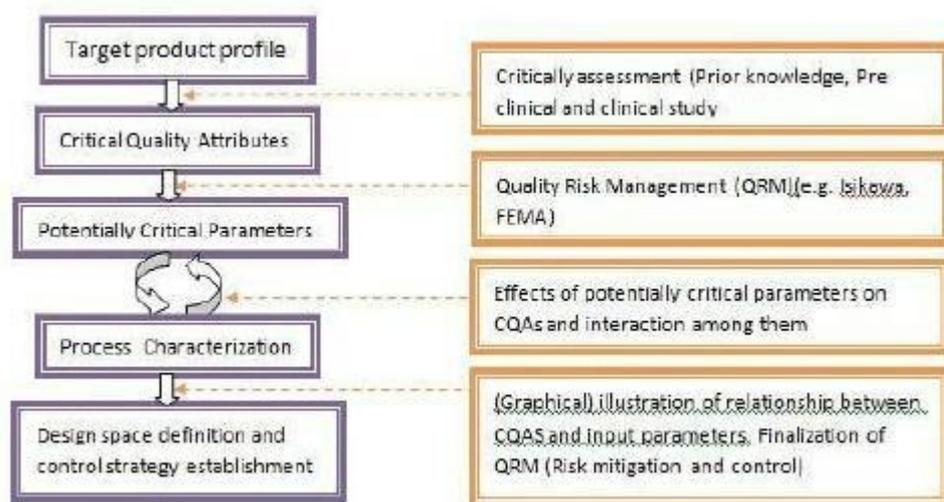


Fig No.3 Simplified Flow Chart of QbD Process

KEY ASPECTS OF QBD

- The Target Product Quality Profile (TPQP) Target Product Quality Profile (TPQP) is a tool for setting the strategic foundation for drug development —“planning with the end in mind.” More recently an expanded use of the TPP in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management has started to evolve.
- Drug Substance and Excipient Properties, To consistently achieve the drug-product quality specified in the label, the drug substance needs to be thoroughly characterized with respect to its physical, chemical, biological, and mechanical properties such as solubility, polymorphism, stability, particle size, and flow properties (20)

THE FOUNDATION OF QbD

ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are foundation of QbD. (21)

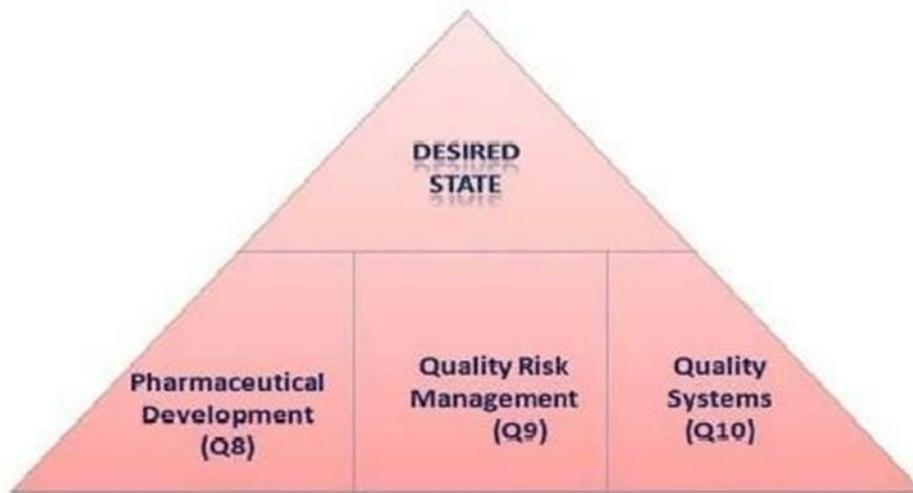


Fig No.4 The Foundation of QbD

Quality by Design relative to ICH20,21

- Concepts aligned
- Design Space - Key to understanding
- Process robustness
- Design of Experiments (DOE)
- Quality management Quality management (22)

Critical Concept: Design Space19-21

- Multidimensional combination with interactions
- Multidimensional interactions put variables (e.g. raw material attributes) and process parameters
- Demonstrated to provide assurance of quality defined by applicant and reviewed by regulator defined regulator (23)

APPLICATIONS OF QUALITY BY DESIGN (QbD)

Quality by design (QbD)

A comprehensive systematic approach to pharmaceutical development and manufacturing.

In Pharmaceutical Development

To design a quality product and a manufacturing process to consistently deliver the intended performance of the product. (24)

Development of Design Space: Science based Product and Process Design in Development

- Enhance process understanding to support science based approach
- Integration of drug substance and drug product process development at the interface.
- Drug substance properties designed for downstream manufacturing process (25)

Utilization of Design Space: Effective Process Control and Quality System

- Use of extensive monitoring during development to enhance process understanding.
- Use science based control during manufacturing.
- However, process control may be limited by time

- needed for biological assays. (26)
- Process Analytical Technology (PAT) is an integral part of Quality by Design**

- Used in development to gain process understanding
- Implemented in routine manufacturing to monitor process, control product quality and reduce release testing control
- PAT testing can replace additional laboratory testing (27)

BENEFITS OF IMPLEMENTING QbD FOR FDA

- 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 for CMC).
- Provides for more flexibility in decision making.
- Ensures decisions made on science and not on empirical information .
- Involves various disciplines in decision making.
- Uses resources to address higher risks. (28)

Benefits to Industry

- Ensures better design of products with less problems in manufacturing.
- Reduces number of manufacturing supplements required for post market changes –rely on process and risk understanding and risk mitigation.
- Allows for implementation of new technology to improve manufacturing without regulatory scrutiny.
- Allows for possible reduction in overall costs of manufacturing –less waste.
- Ensures less hassle during review –reduced deficiencies –quicker approvals.
- Improves interaction with FDA –deal on a science level instead of on a process level.
- Allows for continuous improvements in products and manufacturing process.(29)

CONCLUSION

The goal of a well-characterized method development effort is to develop a reliable method that can be demonstrated with a high degree of assurance to consistently produce data meeting predefined criteria when operated within defined boundaries. During method development, all potential factors (the inputs) and all critical analytical responses (the outputs) are studied to determine the relationships. Critical analytical factors are identified in an approach that parallels what is described for process development in ICH Q8 and Q9. The QbD process on an active partnership of analytical scientists at both the development and operational laboratories as methods are developed and as factors that lead to potential method failures are identified and controlled. A corporate knowledge repository is required throughout the process to ensure critical information is captured that can be reviewed and added to in the future such that lessons learned can be applied to the specific method under consideration and also to other similar methods being applied to other products. Such a repository (in line with concepts described in the draft ICH Q10) will enable continuous improvement and change control of the method to take place throughout its lifecycle.

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