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ENHANCING PHARMACEUTICAL DEVELOPMENT: A COMPREHENSIVE REVIEW OF QUALITY BY DESIGN (QBD)

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ABSTRACT

The contemporary strategy for pharmaceutical quality is called Quality by Design. It explains how to apply Quality by Design to guarantee pharmaceutical quality. This review outlines Quality by Design and identifies some of its components. Each unit operation's quality attributes and process parameters are determined. The advantages, possibilities, and procedures associated with pharmaceutical product quality by design are explained. Q8 for pharmaceutical development, Q9 for quality risk management, and Q10 for pharmaceutical quality systems are the ICH Guidelines that serve as its foundation. Additionally, it explains how Quality by Design can be used to pharmaceutical research and manufacture. The goal of pharmaceutical development is to create high-quality products and manufacturing processes that reliably produce the desired results. Products cannot be assessed for quality; instead, quality ought to be incorporated into the design. It contains important quality criteria, the Quality target product profile, and important facets of Quality by Design. Additionally, it compares the quality of products via Quality by Design and by final product testing. The ICH Guidelines serve as the cornerstone of Quality by Design.

Keywords: Quality By Design (Qbd), Process Analytical Technology (PAT), Quality Target Product Profile, Critical Quality Attributes.

I. INTRODUCTION

"Quality cannot be tested into the product, but it should be built into it," is the fundamental tenet of QbD. The definition of the design space is a equipment, materials, operators, and manufacturing conditions in the product's manufacturing location. Before receiving regulatory permission, the design space needs to be well specified. While working outside of design space is regarded as a change, working with design space is not. When manufacturing takes place outside of the design space, several factors are tracked to see how they affect the quality of the final product. As a tool for QbD, all of these variables are evaluated, and conclusions are reached. The dossier for the regulatory filing contains all of these details. The information gathered from product development studies can be used to develop the formulation of medicinal products. The variables used in QRM will be those that surface during the development phases. Prior to carrying out the development research, the QTPPs of the ultimate product quality must be considered while determining the product, and evaluation is carried out to achieve the required level of product quality. Design space, specs, and manufacturing controls are all included in the product's QTPP. [1,3]

Designs: [4,5]

- The product is made to satisfy both performance standards and patient needs.
- It is known how initial raw materials and process variables affect the quality of the final result.
- The main causes of process variability are located and managed.
- To ensure constant quality throughout time, the procedure is continuously reviewed and modified.

Opportunities: [7, 8]

- 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

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Definition [ICH Q 8(R1)]:

A methodical approach to development that prioritizes product and process insight and starts with predetermined goals and process control, founded on high-quality risk management and solid science. [6]. In order to ensure the safety of the finished product, a system for designing, assessing, and managing production through timely measurements (i.e., during processing) of essential quality and performance attributes of new and in-process materials and processes is needed. [5, 6]

A better scientific understanding of critical process and product qualities, designing controls and tests based on the scientific boundaries of understanding during the development phase, and applying the knowledge gained during the product's life-cycle to work on a continuous improvement environment are all included in the concept of "Quality by Design" (QbD). In order to maintain the required level of product quality, QbD refers to a pharmaceutical development method that includes formulation of the subject's knowledge in an autonomous and cohesive manner, rules and mathematical models are employed.

Benefits of QbD [1,3,5,6]

- 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

STEPS INVOLVED IN QUALITY BY DESIGN PRODUCTS: [7-9]

Development of new molecular entity

- Preclinical study
- Nonclinical study
- Clinical Study
- Scale up
- Submission for market Approval

Manufacturing

- Design Space
- Process Analytical Technology
- Real time Quality Control

Control Strategy

- Risk based decision
- Continuous Improvement
- Product performance

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.
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.

QUALITY TARGET PRODUCT PROFILE: [10, 11]

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

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- 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

In order to establish formulation strategy and maintain the formulation effort focused and efficient, the drug product should have the quality characteristics (attributes) listed in the label guide. This is a logical extension of the Target Product Profile for product quality. It makes it easier to determine what the patient or consumer needs or finds vital in the Quality Target Product Profile (e.g., vital Quality Attributes, CQAs).

Quality by design (QbD) and well understood product and processes: [4,7,8]

- 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.

Qbd by Pharmaceuticals: [8-10]

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

Systematic approach to development:

- That begins with predefined objectives
- Emphasizes products and process understanding
- Process control

Critical Quality Attributes: [12-14]

- 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 theproduct.
- 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.

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Certain Key Aspects of QBD: [15-17]

• 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.

• Formulation Design and Development Not all prototype formulations can be evaluated in human subjects, which mean that developing sensitive in vitro dissolution methods is crucial to an effective development program.

• Manufacturing Process Design and Development Process development and formulation design cannot be separated because a formulation cannot become a product without a prescribed process. Process design is the initial stage of process development, in which an outline 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 design of the process, including facility, equipment, material transfer, and manufacturing variables. Other factors to consider during process development are the QTPP and CQAs.

Product quality by end product testing vs QbD: [17,18]

Successful adoption: [17,18]

- Regulatory flexibility to accommodate quality by design submissions
- Common dossier accepted worldwide by regulatory agencies
- Post-approval changes within pre-defined design space can be implemented with regulatory flexibility
- Laws and processes in place to protect intellectual property (IP)

Designed to consistently meet desired product quality: [17-19]

- Design space concept
- Experimentally defined process operating space basedon scientific principles.
- Critical process parameters identified.
- Critical - impact product quality.
- Space - operating range yielding acceptable product Space.
- Critical process parameters are consistently controlled.
- Product of process is always desired quality Product.
- End product testing might be reduced.

Designed to facilitate continuous improvement: [17,18]

- Process control strategy: control of the process.
- Performance and continuous process improvement.
- Real-time process feedback Process improvements within design space Knowledge builds with experience Leverage information/new technologies to improve process efficiency Key opportunity to continuously improve the process. E.g. increased supply, more efficiency

ICH Q8, Q9, Q10 Guidelines: The Foundation Of Qbd: [2,3,6,18]

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

Quality by Design relative to ICH: [20,21]

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

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Critical Concept: Design Space: [19-21]

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
- Once design space is approved, regulatory post approval change requirements will be simplified
- approval Inside vs. outside design space Inside space
- Regulatory flexibility to operate within the design space Regulatory space

Applications Of Quality By Design (Qbd): [7,8,10,22,23]

Quality by design (QbD)

A comprehensive systematic approach to pharmaceutical development and manufacturing Advancement in the pharmaceutical development and manufacturing by Qbd can be explained against traditional approach

In Pharmaceutical Development

To design a quality product and a manufacturing process to consistently deliver the intended performance of the product

In life cycle management

Continual improvement enabled within design space

QBD In Cmc Review Offices 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

II. CONCLUSION

A well-defined method development effort aims to create a trustworthy technique that, when used within specified parameters, can be shown to reliably generate data that satisfies predetermined requirements. Analytical method development and assessment can benefit from the application of QbD. In order to ascertain the relationships, every critical analytical response (the outputs) and every potential element (the inputs) are examined during method development. Similar to the process development. Throughout the process, a corporate knowledge repository is necessary to make sure important information is recorded that can be examined and updated later so that lessons learned can be applied to the particular approach being considered as well as to other comparable approaches being applied to other products. According to the ideas outlined in the draft ICH Q10, such a repository will allow for method change control and continual improvement over the course of its existence. Instead of carrying out ICH validation and analytical technology transfer activities, a QbD strategy built on a risk-assessed change control mechanism ought to be used. Technique outlined in ICH Q8 and Q9, critical analytical factors are discovered. A risk assessment must to be carried out each time a procedure is modified. A method evaluation and, if necessary, an equivalency exercise should be carried out to make sure method performance criteria are still met in cases where the change is thought to have the potential to move the method outside of its known design space.

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