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EMERGING ACHIVEMENTS OF QUALITY BY DESIGN IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

The present review mainly focused on a quality by design and its aspects in pharmaceutical industry and also deals with the elements in QbD and enablers of quality by design. Quality by design (QbD) is an innovative product development process approach using both existing knowledge and emerging science to identify key "quality" issues. QbD is a systematic, scientific, risk based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control. 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.

KEYWORDS: QbD, ICH Guidelines, Quality, product development, pharmaceutical industry, HACCP.

INTRODUCTION

Quality by Design (QbD) This concept was initially introduced by well-known quality expert Joseph M. Juran on Quality by Design (J.M.: "Juran on Quality by Design",). In the late 1990 FDAs internal discussion began and in the year 2002 the concept paper on 21st century Good Manufacturing Practice was published. With help of several biopharmaceutical companies, pilot programs were started to explore Quality by Design application and its understandings.[1,2]

Quality by design (QbD) is an innovative product development process approach using both existing knowledge and emerging science to identify key "quality" issues (in regulatory jargon, the chemistry/manufacturing/control (CMC) of a medicine) in order to address or predict their impact on product attributes and ultimately patients' health. This can enable a certain freedom to manoeuver manufacturing parameters of a product within a pre-approved design space while they happen during manufacture, without consulting regulatory agencies upfront. The concept of QbD was mentioned in the ICH Q8 guideline, which states that "quality cannot be tested into products, i.e., quality should be built in by design" According to ICH Q8 QbD is defined 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.[3] QbD encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications.

The Food and Drug Administration (FDA) Office of Generic Drugs (OGD) has developed a question based review (QbR) for its chemistry, manufacturing andcontrols (CMC) evaluation of Abbreviated New Drug Applications (ANDAs). QbR is a new quality attributes. It is a concrete and practical implementation of some underlying concepts and principles outlined by the FDA's Pharmaceutical CGMPs for the twenty-first century and quality by design (QbD) initiative.[4]

Advantages of QbD

- It increases efficiency of pharmaceutical manufacturing processes and reduces manufacturing costs and product rejects.
- It provides a higher level of assurance of drug product quality.
- It offers cost savings and efficiency for the pharmaceutical industry.
- It makes the scale-up, validation and commercialization transparent, rational and predictable.

Traditional approach & Enhanced QbD approach

Table 1: Traditional approach & Enhanced QbD approach.

Aspects	Current	QbD
Pharmaceutical Development	Empirical, Random, Focus optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, managed by company's quality systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release possible

Pharmaceutical Quality by Testing: In this system, product quality is ensured by raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in-process material testing, and end product testing. The quality of raw material including drug substance and excipients is monitored by testing. If they meet the manufacture's proposed and FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for manufacturing of the products. Because of uncertainty as to whether the drug substance specification alone insufficient to ensure quality, the drugsubstance manufacturing process is also tightly controlled. A change to the drug substance manufacturing process may require the drug product manufacturer to file supplements with the FDA. Finished drug products are tested for quality by assessing whether they meet the manufacturer's proposed and FDA approved specification.[5]

Pharmaceutical Quality By Design

ICH Q8 defines quality as the suitability, of either a drug substance or drug product for its intended use. This term includes suchattributes as the identity, strength and purity. Pharmaceutical QbD is a systematic, scientific, risk based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives.[9] QbD identifies characteristic that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with desired characteristics. In order to do this the relationship between formulation and manufacturing process variables (including drug substance and excipientsattributes and process parameters) and product characteristics are established and sources of variability identified.

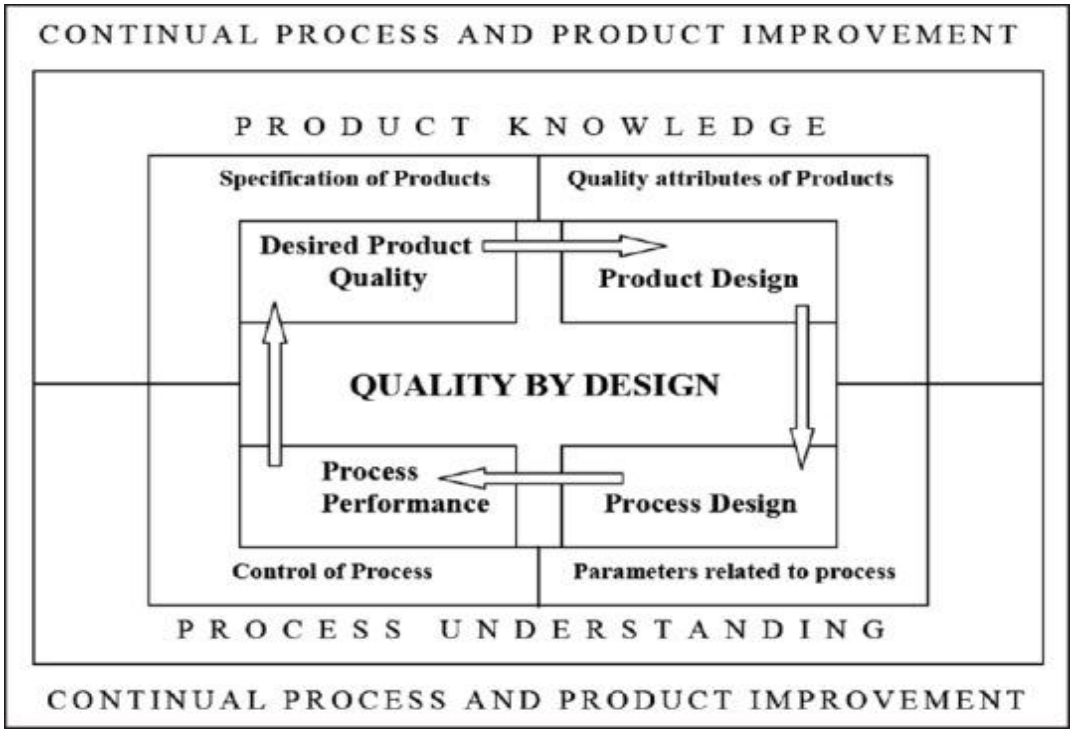

Fig. 1: Quality by design system.

Quality Risk Management

Quality risk management (QRM) is a key enabler for the development and application of QbD. During development, it enables resources to be focused on the perceived critical areas that affect product and process. It is one of the tools that provide a proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality.[6] It also facilitates continual improvement in the product and process performance throughout the product life cycle.

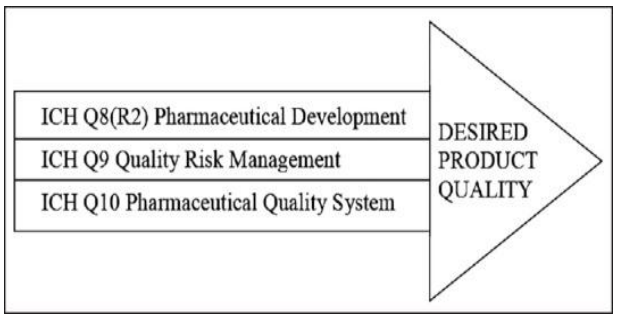

Fig 2: Pharmaceutical quality systems for quality by design.

Elements of Quality By Design

ICHQ8: Pharmaceutical Development discusses the various elements of quality by design. These in combination with the enablers form the fundamental basis for the QbD approach to development. This section describes the various elements in detail and provides examples of the elements for controlled release (CR) products.[7] Certain Key Aspects of QBD Include.

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. The TPP can play a central role in the entire drug discovery and development process such as: effective optimization of a drug candidate, decision-making within an organization, design of clinical research strategies, and constructive communication with regulatory authorities. TPP is currently primarily expressed in clinical terms such as clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, over dosage, etc. TPQP is related to identity, assay, dosage form, purity and stability of Tablet Characteristics, Identity, Assay and Uniformity and Dissolution.[8]

Identifying CQAs

Once TPP has been identified, the next step is to identify the relevant CQAs. A CQA has been defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality". Identification of CQAs is done through risk assessment as per the ICH guidance Q9. Prior product knowledge, such as the accumulated laboratory, nonclinical and clinical experience with a specific product-quality attribute, is the key in making these risk assessments.

Quality risk management (QRM): QRM is an essential part of QbD as it helps in determining the extent of

impact of critical material attributes (CMA) and critical process parameter (CPP) on CQAs, which may eventually assist in prioritizing the CQAs. They are particularly important in complex processes especially that are involved in cases of biologics or bio-similar. FDA defines QRM as a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle.[9] The goals of QRM is therefore to identify risks within a process or event, analyzing the significance of these risks, and take appropriate measures to mitigate such risks if deemed unacceptable.

Enablers of Quality by Design

Quality risk management and Knowledge management is two main of enablers of QbD They play a vital role in development and implementation of QbD. They are instrumental in achieving product realization, establishing and maintaining a state of control and finally facilitating continual improvement.[10]

Quality Risk Management

Quality risk management (QRM) is the basic enabler for Quality risk management (QRM), it enables resources to be focused on the perceived critical areas that affect product and process. It is one of the tools that provide a proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality. It also facilitates continual improvement in the product and process performance throughout the product life cycle. Knowledge Management Product and process knowledge management is an essential component of quality by design and must be managed from development through the commercial life of the product, including discontinuation.[11] It is a systematic approach to acquiring, analyzing, storing and disseminating information related to products, processes and components.

FDA suggest various tools that can be applied for QRM, among which the relevant ones are discussed below: Failure mode effects analysis (FMEA): FMEA is one of the most widely used risk-assessment tools in the pharmaceutical industry. This is systematic and proactive method to identify and mitigate the possible failure in the process. Failure modes represent any errors or defects in a process, material, design, or equipment. Once failure modes are established, FMEA tool evaluates the effect of these failures and prioritizes them accordingly. Risk control activities can then be performed to avoid such failures modes. Since FMEAs require a good understanding of cause and effects, a thorough process understanding is essential.[12]

Fault tree analysis (FTA)

The fault tree analysis (FTA) was first introduced by Bell Laboratories and is one of the most commonly used methods in system reliability, maintainability and safety analysis. FTA is a deductive analysis approach for resolving an undesired event into its causes in a top down fashion.[13] In this method failures are listed at the top as main event and all of the associated elements in that system that could cause the event are listed as subsequent branches till the root condition or cause is identified.

Hazard analysis and critical control points (HACCP)

HACCP provides detailed documentation to show process or product understanding through identifying parameters to control and monitor. The definition of hazard includes both safety and quality concern in a process or product. HACCP consists of the following seven steps:

- Conduct a hazard analysis and identify preventive measures for each step of the process,
- Determine the critical control points,
- Establish critical limits,
- Establish a system to monitor the critical control points,
- Establish the correctiveaction to be taken when monitoring indicates that the critical control points are not in a state of control,
- Establish system to verify that the HACCP system is working effectively, (vii) establish a record-keeping system.

Design Space

ICH Q8 (R1) defines design space as, the multidimensional combination and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality. The design space is proposed by the applicant and is subject to regulatory assessment and approval, it is scale and equipment dependent, the design space determined on the laboratory scale may not be relevant to the process at the commercial scale. Therefore, design-space verification at the commercial scale becomes essential unless it is confirmed that the design space is scale-independent.[14] Currently, generic drug sponsors obtain information about acceptable ranges for individual CPPs and CMAs at laboratory or pilot scales.

Control Strategies

ICH Q8 (R1) defines control strategy as: "A planned set of controls, derived from current product and process understanding that ensures process performance and product quality". The controls may include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control. The control strategy may include Control of raw material attributes (e.g., drug substance, excipients and primary packaging materials) based on an understanding of their impact on process-ability or product quality, Controls for unit operations that have an impacton downstream processing or end-product quality (e.g. The impact of drying on degradation, particle size distribution of the granulate on dissolution), Procedural controls, Product

specifications.[15] The Control Strategy should establish the necessary controls based on patient requirements to be applied throughout the whole product life cycle from product and process design through to final product, including API and Drug Product manufacture, packaging and product life cycle from product and process design through to final product, including API and Drug Product manufacture, packaging and distribution.

Life cycle Management and Continuous improvement

In the QbD paradigm, process changes within the design space will not require review or approval. Therefore, process improvements during the product lifecycle with regard to process consistency and throughout could take place with fewer post approval submissions. In addition to regulatory flexibility, the enhanced understanding of the manufacturing process would allow more informed risk assessment as per ICH Q9 regarding the affects of process changes and manufacturing deviations (excursions) on product quality.[16]

Tools of Quality by Design of Experiments (DOE)

Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. It has been observed that DOE can offer returns that are four to eight times greater than the cost of running the experiments in a fraction of the time. Application of DOE in QbD helps in gaining maximum information from a minimum number of experiments. When DOE is applied to a pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness.[17] DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those who do not, as well as details such as the existence of interactions and synergies between factors Factor at a time and Design of experiments.

Process Analytical Technology (PAT)

PAT has been defined as "A system for designing, analyzing, and controlling manufacturing through measurements, during processing of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality". The goal of PAT is to "enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design." The design space is defined by the key and critical process parameters identified from process characterization studiesand their acceptable ranges. These parameters are the primary focus of on-, in- or at-line PAT applications. In principle, real-time PAT assessments could provide the basis for continuous feedback and result in improved process robustness.[20] NIR act as a tool for PAT and useful in the RTRT (Real Time Release Testing) as it monitors the particle size, blend uniformity, granulation, content uniformity, polymorphism, dissolution and monitoring the process online, at the line and offline, thus it reduces the release testing of the product.

Risk Management Methodology

Quality Risk Management is defined as "A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle". Risk assessment is a helpful science-based method, used in the quality risk management that can help in identifying the material attributes and process parameters that potentially have an effect on product CQAs. Risk assessment is typically performed in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. In QbD, the management should be ensured and provided the risk- and science-based reviews, at critical milestones. For this purpose, the teams have to utilize risk assessment tools in the R&D lifecycle. Risk assessment tools can be used to identify and level parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and primary experimental data. The pharmaceutical industry and regulators can evaluate and manage risks by using well-known risk management tools.[20,21]

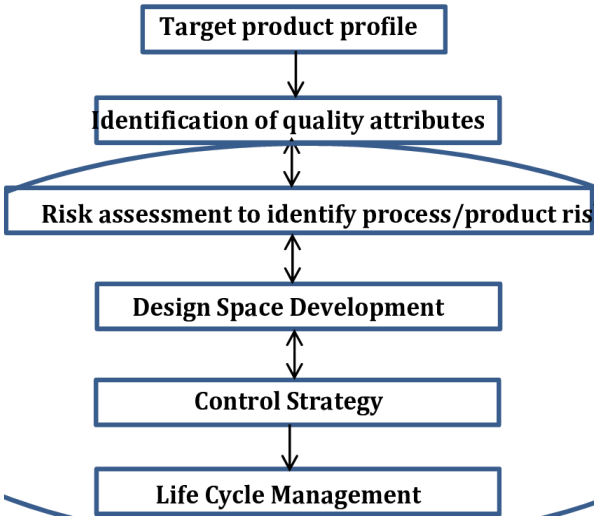

Fig. 3: Enablers of QbD.

Benefits of Implementing QbD for FDA

- Enhances scientific foundation for review
- Provides for better coordination across review,
- 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.
- Pharmaceutical Development
- Widely used in pharmaceutical development and manufacturing

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. The present work mainly discussed about Quality by design and its aspects in pharmaceutical industry and also deals with the elements in QbD and enablers of quality by design Quality by design (QbD) is an innovative product development process approach using both existing knowledge and emerging science to identify key "quality" issues. QbD can be applied to the development and evaluation of analytical methods. 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. This will allow for method improvements to be made via internal change control procedures, and even switches between different techniques (e.g., HPLC versus NIR) may become much easier to implement. This new QbD process offers the opportunity for much greater regulatory flexibility in the future. The method performance criteria could potentially be registered instead of the method itself.

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