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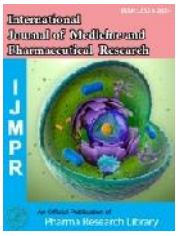

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Pharmaceutical Quality by Design: A Hopeful Ray for Quality Product

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A B S T R A C T

Quality by design is vital part of the modern approach to pharmaceutical quality. The present article gives information about the concept of Quality by Design (QbD) and illustrates how it is helpful to ensure pharmaceutical quality. The elements of quality by design are discussed in this article. The QbD is a systemic approach to design and develop formulation and manufacturing process to guarantee specified product quality. QbD assist to both industry and FDA for pharmaceutical development. QbD approach is based on the concept of building the quality into product not testing it. A company can constantly monitor its manufacturing process to guarantee product quality consistently. QbD provides the scientific configuration to identify all critical attributes of a drug formulation and manufacturing process.

Keywords: Critical Quality Attributes (CQA), Design Space, Quality by design (QbD), Risk assessment, Target Product Quality Profile (TPQP).

A R T I C L E I N F O

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1. Introduction

Quality is nothing but ability to fulfill the needs and expectations of the customer. Customer demands the excellence in quality, consistency, low cost and timely performance. The word quality is originated from Latin word '*qualis*' means 'of what kind'. Quality is having a great importance when it is specifically related with drugs [1]. Pharmaceutical quality can be defined as the product having the pre-specified quality attributes and regulatory specification. The pharmaceutical manufacturing is one of the main strictly regulated and governed sector by

authoritative regulatory bodies, because quality of pharmaceuticals directly related to the health of the public. Therefore there is need to control the quality of pharmaceuticals.

The aim of pharmaceutical industry is to design product and manufacturing process to consistently deliver the quality product with proposed specifications. It is important to be aware of that quality cannot be tested into products; it must be built in the product by design; the concept was summarized by quality expert Joseph M. Juran. The product should be designed to meet patient's needs and the intended product performance which will help the pharmaceutical industries to excel in global competition. [2,3] In quality by testing, raw materials, in process and finished products are tested according to specifications. Finished products are tested for quality to find whether they meet the manufacturers or FDA approved specifications. If not, then final products are discarded, which leads to wastage of money and time. Generally root causes for failure are not understood and resulted in product recalls and drug shortage. Achieve this target QbD is helpful by thorough understanding of process.[4,5]

Quality activities must try to detect quality problems as early as possible to allow actions without requiring compromise in cost, schedule or quality. The emphasis must be given on the prevention of quality problems rather than on correction of it therefore there is need to implement QbD for pharmaceuticals to overcome above mentioned problems. As far as pharmaceutical industry is considered patient safety and provision of quality products have been given prime importance. QbD involves an understanding of effect of product and process variables on product quality. It applies use of a systematic approach to give assurance of quality products by developing a complete understanding of the compatibility of a finished product with all the components and process during manufacturing that product. Instead of finished product testing alone, QbD provides monitoring throughout the development process. As outcome, a quality matter can be professionally analyzed and its root cause rapidly identified.

International Conference on Harmonization (ICH) guidelines related to quality includes: Q8 Pharmaceutical Development the aim of which is to design a quality product and its manufacturing process to consistently bring the intended performance of the product. Q9 Quality Risk Management which presents a systematic process for identification, communication, control and review of risks to the quality of the drug product during the product lifecycle. Q10 Pharmaceutical Quality System, also assist pharmaceutical manufacturers by describing a model for an efficient quality management system for the pharmaceutical industry, Quality by Design (QbD) is incontrovertibly ready to help industry to solve the persistent challenges of drug development and manufacturing. [5]

Definition of Quality by Design [ICH Q 8(R1)]

QbD is defined as, a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and control, based on sound science and quality risk management**. [6]**

2. Advantages of QbD

- Patient safety and product efficacy is focused.
- Scientific understanding of pharmaceutical process and methods is done.
- Critical quality attributes are recognized and their effect on final quality of product is analyzed.
- Well organized use of time and cost of development and increase in revenue.
- Helpful to meet FDA guidelines which reduces approval time and fewer queries from the FDA.
- Less rejection of batches.
- Fewer manufacturing deviations.
- Save hundreds of costly hours.
- Faster time to market and more reliable supply.
- Fewer inspections of manufacturing sites.
- Better development decisions.
- Empowerment of technical staff.
- Incorporate risk management.
- Ensure consistent information. [2,6,8,10,11,12]

Elements Of QbD- [11,16,17,18,19]

1. Defining the target product quality profile
2. Identifying critical quality attributes
3. Performing Risk Assessment
4. Establishing Design Space
5. Defining Control Strategy
6. Life cycle Management, Continuous improvement

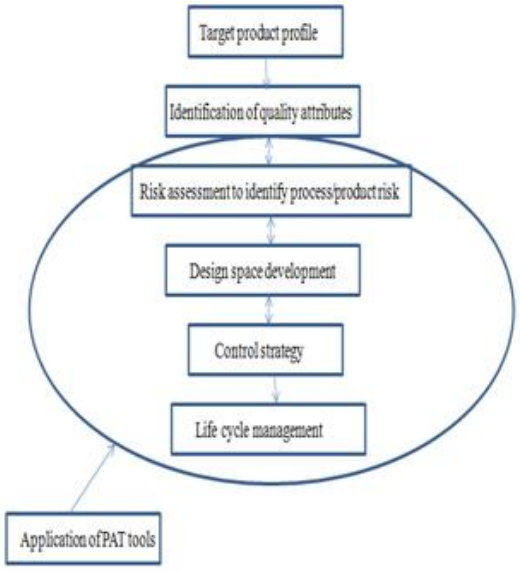

Figure 1: Pictorial representation of the elements of QbD

These elements of QbD are described below briefly.

Defining the target product quality profile (TPQP)

It is nothing but the quality characteristics which the drug product should possess so as to bring the therapeutic benefits reproducibly given in the label and thus the drug product safety and efficacy is realized. This include

- Dosage form,
- Route of administration,

- Strength(s) of dosage form,
- Factors related to Pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance)
- Drug product-quality criteria (e.g., sterility, stability and purity)
- Intended use in clinical setting
- Container closure system.
- Therapeutic moiety release or delivery [3]

Identifying critical quality attributes (CQA)

- The next step is to identify the relevant CQAs after identification of TPQP.
- It can be defined as physical, chemical, biological or microbiological characteristics that should be within an appropriate range to ensure the desired quality product.
- CQAs are associated with the drug substance, excipients, in process materials and product. It is important step to identify the quality parameters that are critical which affect the quality of final product. These attributes are directly related to the safety, efficacy & quality of the product [2]

Performing Risk Assessment

The aim of this step is to identify risks during the process, analyzing the significance of these risks, and take proper measures to prevent such risks. Quality Risk Management (QRM) is essential part of QbD. It helps in identifying effect of critical material attributes (CMA) and critical process parameter (CPP) on CQAs. Risk assessment helps to boost quality of method or process. A risk assessment Is the way for effective communication between industry and FDA, and among different manufacturing sites within company. The assessment of the risk of quality is based on scientific knowledge leads to the therapeutic benefit to the patient. [14]

3. Establishing Design Space

- The next step is to define the product design and design space. It includes specifications for drug substance, in-process material and drug product attributes. These specifications link the attributes to the safety and efficacy of the product.[5]
- Design space can be defined as, the linkage between input variables (material attributes) and process parameters to give assurance of quality. Out of the design space is considered to be a change.
- A design space is a combination of input variables, their interactions and process parameters that have been established to provide assurance of quality. A design space can be constructed for the entire process or single or multiple unit operations. This approach can help to attain overall control of a system.[14,15]

Defining Control Strategy

It can be summarized as a set of controls which are required to be applied during the whole product life cycle, obtained from current product and process understanding and ensures process performance and product quality. The controls may include parameters and attributes related to

- Raw material which include drug, excipients and packaging materials
- Drug product materials
- In-process controls
- Facility and equipment operating conditions
- Finished product specifications
- Frequency of monitoring and control. [13,15]

Life cycle Management and Continuous improvement

It is nothing but continuous improvement throughout products life cycle without changing design space; which means that quality can be improved during whole manufacturing process. Different industries have different strategies based on their manufacturing experience and sound knowledge. In this, Critical quality attributes are monitored to check consistency of quality to guarantee that the process is performing within the defined acceptable variability. [3]

Barriers to Implement QBD

Qbd is having numerous economical and operational advantages even though manufacturing industries are not implementing QbD approach due to following reasons:

- Inadequate understanding of the process and its benefits
- Organizational resistance to change
- It is assumed by the company that QbD require more time.
- Lack of technology to implement QbD.
- Inconsistent treatment of QbD across FDA.
- Lack of concrete guidance for industry.
- Regulators not ready to handle QbD applications.
- Existing regulatory benefits do not inspire to follow QbD.[3]

4. Conclusion

Quality by design is an important part of the systematic approach to pharmaceutical quality. Quality by design is an understanding which is based on ICH Q8, Q9 and Q10 concepts. QbD is helpful during formulation process to assure quality product. This review article describes the use of target product profile, risk assessment, identification the critical quality attributes, implementation of control strategy and continues monitoring and improvement. It can be concluded that Quality by Design (QbD) aspect plays significant role in process understanding and create opportunities for identification of risk and developing control strategy in the formulation and process development.

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