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DEFINE AND DEVELOPMENT OF SMART DRUG TROUGH QUALITY BY DESIGN

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ABSTRACT

The newest approach in pharmaceutical production linked to quality is called Quality by Design to guarantee that premium-grade pharmaceuticals are produced, Pharmaceutical Quality by Design, or is discussed in this article. A description of Quality by Design is provided along with a list of its constituent parts. Every unit activity has its own set of quality metrics. The use of Quality by Design and its associated measures can yield significant benefits for pharmaceutical goods. The foundation of pharmaceutical R&D is high-quality drugs and the procedures used in their production. A product's quality cannot be easily verified because this paper just summarises the product's quality profile and the most important components of Quality by Design. Quality by design and end-product testing are two ways to compare the quality of various goods. Quality by Design is based on the ICH Guidelines. ICH guidelines apply to the development of medications and the application of quality control methods. The research and manufacturing of pharmaceuticals might profit from Quality by Design As the product develops and is designed, it is crucial to determine the desired product performance report under these ideas. The TPP, QTPP, and CQA stand for target product profile.

INTRODUCTION

Quality is an important term in Quality by Design. Therefore, "standard or suitable for intended use" is what quality is. These features of identity, strength, and purity are incorporated in this statement [1]. Quality by Design: - The US-FDA (United States Food and Drug Administration) and the International Council Harmonisation (ICH) have encouraged a number of approaches for the development of pharmaceutical products and their subsequent production. The US-FDA has issued specific QbD guidelines for biotechnology and immediate and timed-release medicinal products. The application of ICH quality criteria is always being recommended by the regulatory bodies. The development of a better product and process that always produces the desired results is the objective of pharmaceutical development. It is important to recognize that products cannot be tested for quality. Instead of testing the final results of the analytical process, quality should be embedded in the process. Among the industries with the most stringent regulations is the pharmaceutical industry. It is always producing high-quality human prescription drugs with pharmacotherapeutic values to provide relief for a variety of diseases [2]. A guideline paper for pharmaceutical companies was published by the US Food and Drug Administration [FDA] in 2002. Products should embody quality, safety, and efficacy. Quality by Design is the new name for this concept. In a 2004 paper, Janet Woodcock, the director of the Centre for Drug Evaluation and Research, described pharmaceutical quality as a product that is free from contamination. They gave the consumer the therapeutic value that the label dependable assured. The QbD approach is a new finding in the development of analytical methods. A drug product that is free from contamination and defects which delivers the labelled therapeutic, pharmacokinetic benefits and reproducibility has high quality. Performance, reliability and durability are the dimensions of quality. Planned quality incorporated into the product is quality by design (QbD). The term quality by design (QbD) was first proposed by Dr. Joseph M. Juran, and it was applied in the automotive industry. Quality by design (QbD) in pharmaceutical sciences was proposed by Food and Drug Administration (FDA) and the International Conference on Harmonization (ICH). The basic concept of quality by design is that 'the quality is

not to be tested into the product, but it should be built into. The pharmaceutical industry works hard to develop, manufacture, and bring to market new drugs-and to comply with regulatory requirements to demonstrate that the drugs are safe and effective. A new approach to drug development could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product's life cycle. This article explores the processes used in developing a market formulation and requisite supportive data, particularly in light of the industry's current movement toward submissions based on quality by design (QbD). The Food and Drug Administration (FDA) Office of Generic Drugs (OGD) has developed a question-based review (QbR) for its chemistry, manufacturing and controls (CMC) assessment of Abbreviated New Drug Applications (ANDAs. This knowledge is then used to implement a flexible and robust manufacturing process that can adapt and produce a consistent product over time [3].

Importance has been given to quality by all the regulatory organizations for the pharmaceutical products. Quality is the customer satisfaction in terms of service, product, and process. Many of these activities related to quality show the need for companies to perform better in the global competition. Customer demands perfection in quality, reliability, cost, and time performance. Customer satisfaction can be achieved by two methods, namely, features and free from deficiencies in the goods. The features such as performance, reliability, ruggedness, ease of use, and serviceability have to be incorporated into the product, and such a product should be free from deficiencies. Quality, productivity, cost, cycle time, and value are interrelated terms. Quality activities should attempt to identify quality problems sufficiently in advance to permit their resolution without compromise in cost, schedule, or quality. Simple analysis of the final product will not be sufficient but the quality should be designed in the product. Product and that too with consistency in the manufacturing process to deliver the intended performance of the product. The information and knowledge acquired from pharmaceutical studies and manface turing act as a basis for scientific understanding to support the establishment of design space, specification, and manufacture in control. The information from pharmaceutical development studies can be a root for quality risk management [4].

HISTRORY OF QBD

In 2007, Deceived 5000 supplements, it was actually a striking increase in the number of manufacturing supplements to applications of New Drug Applications (NDAs), Biological License Applications (BLAs), and Abbreviated New Drug Applications (ANDA's). FDA realized that there is an increase in lapse of NDA or ANDA submissions by the firms, a large number of a supplemental application for every manufacturing change were received. In original applications as well as supplements, the data primarily focused was on chemistry. And the least attention was given on other important aspects of the manufacturing, such as engineering, product development. Finally, the FDA realized that more and more con trolls were required for drug manufacturing processes for drug product and no doubt for better regulatory decision-making [5].

A concept of QbD was founded by well-known quality expert Joseph M. During 1986, W. Edwards Deming (in out of crisis), also interestingly explained the concept of quality by design with the example of disease. In 2002 the FDA announced this initiative intended to modernize the FDA's regulation of pharmaceutical quality and establish a new regulatory framework focused on QbD, risk management and quality systems. QbD requires an understanding of how product and process variables influence product quality [6].

ELEMENTS OF QBD

QbD encompasses all aspects of pharmaceutical development as discussed in the ICH guideline Q8. Pharmaceutical Development section is expected to offer a full understanding of the product and manufacturing process to the reviewers and inspectors. To develop a quality product and its manufacturing process to achieve the intended performance of the product is the objective of pharmaceutical development. The knowledge and information obtained from pharmaceutical development studies and manufacturing experience offer scientific understanding to support the development of the specifications, and manufacturing controls.

– Risk assessment– Development of experimental design
– These aspects of a QbD strategy for advancements that are Now that quality, safety, and efficacy can be linked, the TPP can be improved [7].

1. TARGET PRODUCT PROFILE (TPP)

The TPP describes the acceptable look of a medicinal product with regard to medication development and labelling. The TPP describes the aim, target market, route of administration, and other essential elements besides the high-quality design of the product.

2. TARGET QUALITY PRODUCT PROFILE (TQPP)

In the area of product quality, the term TQPP might be seen as a natural extension of the term TPP. The data that cannot be transmitted from one generation to the next generation needs to be comprehended and traced back through the QTPP [8].

• Clinical Pharmacology
• Indications and Usage

3. IDENTIFICATION OF QUALITY ATTRIBUTES

Critical Quality Attributes (CQA): Certificates of conformity, or CQAs, are used in many different contexts to guarantee a product's efficacy, safety, stability, and quality. To ensure that the final product's quality remains within acceptable parameters, it may also be specified, measured, and monitored. Clinical safety and efficacy are examples of quality qualities, together with the parameter border nearing failure

4. Risk assessment to identify process: [9]
A risk-based evaluation of a technique or process may improve its overall quality. An evaluation of risks is intended to identify the critical components that have an impact on the final product's quality. Methods for risk assessment are as follows.The ICH guideline Q9 outlines some methods for risk estimation, which are:
• Failure Mode Effects Analysis (FMEA).
• Fault Tree Analysis (FTA).
5. CRITICAL QUALITY ATTRIBUTES (CQA)
Certificates of conformity, or CQAs, are employed in a variety of settings to ensure a product's efficacy, safety, stability, and quality. In order to ensure that the quality of the final product is within acceptable limits, it may also be defined, quantified, and controlled. quality qualities, together with the parameter boundary limit approaching failure.
6. CRITICAL MATERIAL ATTRIBUTES (CMAS)
If a product is not able to satisfy a QTPP due to an actual change in a parameter, it is essential that the experiment fails. In the process of identifying which attributes are essential, it is essential to consider both the level of change that one is willing to implement and the unique attributes of each input material.
7. CRITICAL PROCESS PARAMETERS (CPP)
Any processable input or output of a process step must be controlled in order to attain the right procedure consistency and product quality. Every item in this read would have an approach parameter. Prerequisites and in-process parameters that could potentially impact the final product's yield, purity, and attractiveness are assessed.
8. DESIGN SPACE
The relationship between the process inputs and Critical Quality Attributes can be explained by the Design Space. Operating within a design space is not regarded as a change. A design space is described as the "multidimensional combination and interaction of input variables" quality.
Although creating a design space is optional according to FDA rules as product and process knowledge may be obtained without one, a technique like this can help achieve more compassionate product quality and overall system management.
9. CONTROL STRATEGY: A CONTROL STRATEGY CAN INCLUDE
- Control of attributes of input materials based on an understanding of their effect on processability or product quality. E.g. drug substance, excipients, primary packaging materials etc.
- Control of unit operations that affect subsequent processing or product quality. e.g. the effect of drying on degradation, particle size distribution of the granulate on dissolution • In-process or real-time release testing in lieu of end-product testing. E.g. measurement and control of CQAs during processing.

10. CONTINUOUS IMPROVEMENT THROUGHOUT PRODUCT LIFE CYCLE
Product quality can be enhanced at all stages of the product life cycle; companies have the opportunity to choose innovative solutions to enhance quality. Process performance can be tracked to ensure consistency in quality. More experience and knowledge acquired during normal production, which helps in the development of method/process. Peri-odic maintenance can be performed under the company's internal quality management system this is the distinguishing feature of the QbD strategy over the traditional approach, which is a much more frozen process [10].
11. LIFE CYCLE MANAGEMENT
In the QbD philosophy, process changes within the design space do not require review and approval. Thus, process improvements during the product life cycle in terms of process consistency and throughput could be achieved with fewer post approval submissions.
Barriers to QbD 7
1.Culture challenges:
2.Move from prescriptive approach
3.Benfits of implementing qbd
Benefits of applying QbD in FDA 12,13,14
• Improves scientific basis for review
• Allows for better consistency
• Applies resources to higher risks

UTILISING QBD IN THE DEVELOPMENT OF ANALYTICAL METHODS

The pharmaceutical industry is adopting QbD as it helps in the development of robust, sturdy, and resilient methods that are in line with the ICH guidelines. This approach helps in the continuous improvement of the technique. Disintegration studies. Hyphenated technology such as LC-MS. Advanced techniques such as capillary electrophoresis, mass spectroscopy, and UHPLC. Analysis of genotoxic contaminants.

FUNDAMENTAL OF QBD

This requires an understanding of the impact of the development of the formulation process of the product on the quality of the product (Fig. 2). QbD requires understanding the sources of variability and their impact on the final product and then controlling the variability. The quality of the final product is measured by its performance. If QbD is properly followed, then the need for testing of the final product is eliminated

PHARMACEUTICAL QUALITY BY TESTING

The quality of the products is ensured by the testing of raw materials, drug substance manufacturing, fixed drug product manufacturing process, in-process material testing, and end product testing. If they are within the proposed and FDA-approved specifications or other standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products.6 Since a few tablets out of several million

are tested, drug manufacturers are usually expected to conduct extensive in-process tests, such as blend uniformity, tablet hardness, etc; to ensure that the result of in-process testing is also within the FDA-approved in-process testing specifications. The manufacturers are also not allowed to make any changes to the operating parameters specified in the batch record or other process changes without filing supplements with the FDA. Consequently, the FDA has been flooded with the number of Chemistry, Manufacturing, and Controls (CMC) supplements in recent years. For instance, in 2005 and 2006, the FDA Office of Generic Drugs received over 3,000 CMC supplements each year. This fixed process and extensive testing are what ensure quality in the traditional system.

characterization of variability, inadequate understanding to identify and quantify critical process parameters, and caution on the part of regulators leads to a very rigid and inflexible specifications that prohibit the release of products that may have acceptable clinical performance Significant industry and FDA resources are spent debating issues related to acceptable variability, need for additional testing controls, and establishment of specification acceptance criteria. Often these debates are concentrated on acceptance limits or statistical aspects. FDA reviewers' conservatism results from the fact that manufacturers may not understand how drug substance, excipients, and manufacturing processes affect the quality of their products or they do not share this information with FDA reviewers. In summary, product quality and performance are, in the traditional framework, accomplished primarily through limiting flexibility in the manufacturing process and through end product testing.

FORMULATION DESIGN AND DEVELOPMENT

Not all prototype formulations can be assessed in human studies, which means that the development of sensitive in vitro dissolution tests is essential to a successful development program. The FDA-recommended in vitro dissolution test is typically used for quality control. Generic drug sponsors have indicated that they have in-house methods for pharmaceutical development (some of which have indicated that they use as many as five biorelevant dissolution conditions) prior to conducting bioequivalence studies. QbD should focus on the relevance of individual studies rather than the number of studies because one of the goals of QbD is to understand the material attributes of the drug substance and excipients on product quality. [25] In order to develop a robust generic product that possesses the desirable QTPP, a product development scientist must seriously consider the biopharmaceutical properties of the drug substance. Biopharmaceutical properties encompass physical, chemical, and biological properties. Physical properties include physical description (particle size, shape, and distribution), polymorphism, and aqueous solubility as a function of pH, hygroscopicity, and melting points [11].

MANUFACTURING PROCESS DEVELOPMENT

Process development and formulation design cannot be separated because a formulation cannot become a product without a prescribed process. Process design is the first stage of process development, in which an outline of the commercial manufacturing processes is documented, including the 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. Depending upon the product being developed, type of process, and process knowledge the development scientists have, it may be necessary to conduct preliminary feasibility studies before completing the process development. The selection of the type of process depends upon the formulation and the properties of the materials. Direct compression is the most simple, easiest to control, and cheapest method of tablet manufacturing. It requires only two major unit operations: mixing and compression. Direct compression is used when the ingredients can be mixed, placed on a tablet press, and formed into a high-quality tablet without having to alter any of the ingredients. If the powders are very fine, fluffy, won't stay mixed together, or won't compress, then they need to be granulated. Granulation is the process of gathering particles together by forming bonds between them [12].

QUALITY RISK MANAGEMENT

Risk management, as stated by the FDA, is a strategic safety program that employs intervention (or) instruments to minimize product risk. The risk to the quality of drugs is evaluated, controlled, and reviewed by a systematic process that covers the entire life cycle of the product. The clinical department, manufacturing, sales and marketing, regulatory affairs, and quality unit are all collectively responsible for risk management.

CURRENT APPROACH IN QBZ

Quality is ensured by testing and inspection.

It includes only data intensive submission which includes disjointed information without "big picture". Here, any specifications are based on batch history.

Here there is "Frozen process," which always discourages changes. It focuses on reproducibility which often avoids or ignores variation

Quality is built into product & process by design and based on scientific understanding.

It focuses on robustness which understands and control variation.

APPLICATIONS OF QBD [13]

QBD has been used in pharmaceuticals, biopharmaceuticals, clinicals, and genetics. Examples of applications of QBD are given below.

11.1 in solid oral dosage form

Understanding Drug Properties in Formulation and Process Design of Solid Oral Products', discuss scientific and technical principles related Product and Process Design and development for pharma cuticle product. This is in line with the basic principle of QbD [14].

11.2 In gel manufacturing

High-throughput tools and ap preaches for development of process chromatography steps which are used for purification of biotechnology products. Hence separation of the various entities that are present at the microbial fermentation or mammalian cell culture, stages of process development are focused [15].

11.3 challenges and solution for application of qbd to biopharmaceutical

The manufacturing of biotech product is a process that involves a number of complex steps, therefore there are a number of quality attributes to be controlled, according to his article Quality by Design for biotechnology products: challenges and solutions [16].

CONCLUSION

QBD has gain importance in the area of pharmaceutical pro cesses like drug development, formulations, analytical method and biopharmaceuticals. The main reason behind adoption of QBD is the regulatory requirements. Pharmaceutical industry needs a regulatory compliance so as to get their product ap proved for marketing. Never the less QBD approach gives qual its product with cost effective procedures and that is the basic need. QBD replaces previously used frizzed approach of pro cess development by providing a design space concept. Moving within design space would not require post approval changes thereby reducing the cost involved. QBD approach to generic drug products from January 2013 is recommended. QBD becomes important in the area of pharmaceutical processes like drug development, formulations, analytical methods and biopharmaceuticals. The major reason behind adoption of QBD is the regulatory requirements. Pharmaceutical industry requires a regulatory compliance to get their product official for marketing.

AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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The authors have no conflicts of interest to declare.

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