

Quality By Design- A tool for quality management

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ABSTRACT

Quality by Design is the modern approach that ensures the quality of the product. The idea of QbD has already uprooted the ongoing industry and in the future it will give successful boost to emerging industries. The main objective of QbD is that it focus on drug efficacy as well as safety of patients. QbD provides less batch failure and also provides proper use of drug. The major tools of QbD are Target Product Profile, Design of experiment, PAT, Risk assessment tools. QbD provides some of the opportunities like it not only reduces the cost but also increases manufacturing efficiency. ICH guidelines of QbD are Q8, Q9 and Q10. Some of the applications of QbD are like that it provides better interaction with industries and provides scientific knowledge of drug

1. INTRODUCTION

In pharmaceuticals or any other manufacturing unit, quality of any product is very important and quality is defined as the state that is free from any defects, any errors, and that satisfies customers requirement in all terms and process. Now a days, its the time of competition, not only in pharmaceutical sector but in every sector and that's why it is very important to achieve a product of high quality. Pharmaceutical industries should have to have a product of higher quality as they deals with the lives of thousands of people. Evaluation of quality can be done by

some of the approaches like first is Quality only and other ones are Quality Control (QC), Quality Assurance (QA) and Quality Management (QM)[1]. In modern time, the scientific approach to check the quality, design of any product is done by Quality by Design (QbD) [2]. QbD is firstly introduced by Joseph M. Juran. QbD is the process that ensures the quality of the product. QbD not only focus on drug efficacy but also on patient's safety [3]. Quality by Design works on process development and product design and its safety. QbD is there to ensure a predefined quality, QbD has its importance in manufacturing as well as in developing formulations. The tools that can be used in QbD are DOE i.e Design of experiment, Process analytical technology and risk assessment [3]. There are some of the guidelines of ICH that explained the principles of QbD which includes risk management, method of designing of any product etc. These ICH guidelines are ICH guideline Q8, 2012, ICH guideline Q9, 2012 and ICH guideline Q10, 2012. Some of the applications of QbD are like it mainly deals with the safety of patient and the main thing is that in this QbD we can identify the quality of the critical products. In this process there are less batch failure problems and one can have a better understanding of the process [4]. The main objective of this QbD is that for a novel modified release of any solid dosage form how should we can improve the robustness of a core tablet [5]. The main elements of QbD are:

- TPP (Target Product Analysis)
- QTPP (Quality Target Product analysis)
- Design space, CQA (Critical quality attributes)
- PAT (Process analytical technology)
- QRM (Quality Risk Management)
- QRA (Quality Risk Assessment)
- CPP (Critical Process Parameter).

Quality by Design helps in many aspects like it helps in continuous improvement of the pharmaceutical products in every conditions, by this methodology one can justify and identify the target product profiles, product and process understanding [6]. QbD is different for both NDA (New Drug Application) and ANDA (Abbreviated New Drug Application) products and

their difference is most apparent at the step of process. The target product profile for an NDA is under development but in the case of ANDA the target product profile is established.

2.EVALUATION OF QUALITY

Evaluation of quality can be done in following ways:



Figure 1: Evaluation Parameters of Quality.

2.1 Quality: Quality is defines as the state that is free from any contamination, any defects, any errors and the one that satisfies the customer's needs and requirements in all ways and process. It can also be defined as the degree of excellence.

2.2 Quality Control: Quality Control is basically defined as the procedure that ensures that a manufactured product adheres to define all the quality criteria or also that meets the requirements or needs of the customer [7].

2.3 Quality Assurance: Quality Assurance is basically done before the work is completed. Quality Assurance is defined as the procedure that ensures that a service or any given product is under procedure [7].

2.4 Quality Management: Quality Management is the procedure in which one can manage to maintain a task to its desired level of excellence. Quality Management can also be referred as Total Quality Management (TQM).

3. CONCEPT OF QbD and BACKGROUND

Quality by Design which is a scientific method to make a product that must have guarantee of safe, efficient and cheap drug supply to customer and also to improve quality performance of manufacturing. This concept of QbD was first given by Joseph M. Juran. He published it in his various publications also. According to Joseph M. Juran to meet the product of high quality firstly we should have to plan quality. In various guidelines the concept of this QbD has been mentioned like ICH guideline Q 08, ICH guideline Q 09 and ICH guideline Q10. In 1990, Quality by design aspect was shown by many of the medical devices [3]. In 2002, FDA, through pharmaceutical cGMP (Good manufacturing practice) makes some changes for 21st century. Then, In 2005 firstly QbD was implemented for systemic approach. Now in 2013 Fda indicates warning for generics to implement QbD in their products [1].

4. OBJECTIVES OF QbD

The main objectives of QbD are as given below:

- The main objective of QbD is to focus on drug efficacy and also on patient's safety.
- QbD works on process development and product design and its safety.
- QbD has also its importance in manufacturing as well as in developing formulations.
- During development it ensures the knowledge gained through the combination of product and process development.
- Desired attributes can also be constructed through this knowledge.

- Thorough design space experimental study can be viewed as positive performance testing of the model.

5. REGULATORY ASPECTS OF QbD (FDA)

Recent ICH quality guidelines are:

- ICH Quality guideline Q8
- ICH Quality guideline Q9
- ICH Quality guideline Q10

ICH Quality guideline Q8

- For pharmaceutical product development, it describes good practices.
- Concepts of design space and flexible regulatory approaches are introduced by this guideline.
- It elaborates the QbD concepts.



Figure 2 : Qbd (as per Quality guideline Q8)

ICH Quality guideline Q9 (Quality risk management)

- A systemic procedure for quality, assessment, review of quality risk and communication is described by this guideline.
- It can be applied over lifecycle of product i.e. development, manufacturing and distribution.



Process Development

Control Strategy Development

Continual Improvement

Figure 3: List of steps in Quality risk management

ICH Quality guideline Q10

- This guideline is basically applied to drug substance as well as drug product throughout its lifecycle
- Continual Improvement is facilitated by this guideline.
- It describes the system the facilitate as well as maintain product quality [8].



Figure 4 : Steps of Product discontinuation as per ICH guideline Q10

6. Benefits Of QbD

Benefits of QbD are as follows:

- QbD basically provides a better understanding of a manufacturing process, it also introduces some additional steps to initial stages of development process of any product.
- It assures the safe and effective use of drug for consumers and patients.
- It leads to reduction of post-approval submissions.
- Less batch failure.
- It also provides improved yields, less investigations, reduced testings and low costs of drugs [9].
- It can also facilitate real-time release testing or real time controls (less batch failure).
- Science based assessments is carried by this QbD [1].
- This QbD involves designing of product as well as process development.
- It determines the dependencies of product quality on variations in process [10].
- It provides more drug availability and less recall.
- It also provides opportunities for more flexible regulatory approach.
- Also provides greater drug consistency for patients [1, 10].

7. Opportunities of QbD

- Better interaction with industry
- It can build the scientific knowledge of products
- Risk management is incorporated
- It can reduce cost along with this it also increases manufacturing efficiency
- Ensure consistent information of the product

8. Traditional versus QbD approach

Aspects	Current	QbD
Pharmaceutical Development	Empirical and Random	Systemic
Manufacturing Process	Fixed	Adjustable within design space
Control Strategy	Can be done by testing and	Control strategy risk based

Process Control	inspection Some in-process testing	Process operations
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9. Steps of QbD

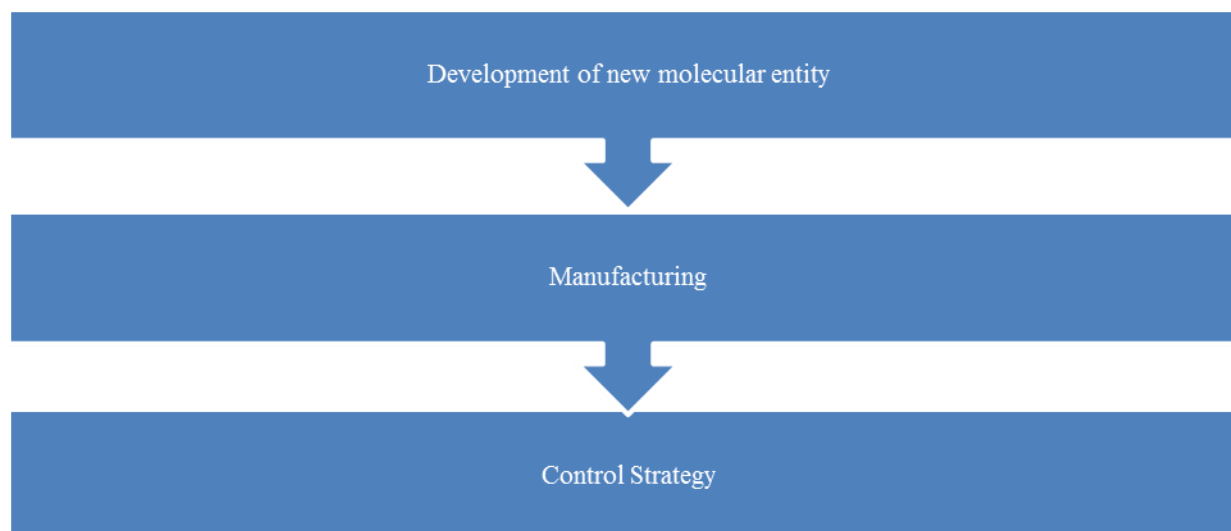


Figure 5: Steps followed in QbD

1. To develop a molecule entity:
 - Preclinical Study
 - Nonclinical Study
 - Clinical Study
 - Scale up
 - Submission for market Approval
2. Manufacturing :
 - Design Space
 - Process Analytical Technology
 - Real time quality control
3. Control Strategy :

- Risk based decision
- Continuous Improvement
- Product Performance [11]

10. Elements of QbD

10.1 Target Product Profile (TPP) : The overall time or intent of development of drug can be defined by TPP. It also provides information at the particular time during the development of drug. During labeling of any drug this TPP is usually organized according to the key sections. According to ICH Q8, any pharmaceutical development should include the identification of all the things that are critical to quality of drug, it must include the considerations of intended use of drug product as well as the route of administration of that drug product (i.e. through TPP) [12].

Generic version of drug and also the reference of that product should have same TPP as it can be thought as “user interface” of drug. For a new product that to be launched into market TPP may require safety and efficacy but if there are some changes in the same product then there is not any change that has to be made. Mainly TPP includes the route of administration of drug, dosage form and dosage size, physical appearance of drug, type of patient the drug has to be delivered) [12].

10.2 Quality Target Product Profile (QTPP): QTPP is an essential part of QbD and it provides the basis of design for development of drug. It basically provides the information of that which provides the safety, efficiency and quality of the drug product that is essential for the patient.

Considerations for QTPP includes:

- Quality Criteria of drug products that include sterility, stability and purity.
- Closure system of the container of the drug product
- Route of administration of drug
- Intended use of drug product
- Dosage form and Dosage strength of drug product [12]

10.3 Critical Quality Attributes (CQA): CQA of every dosage form is different in some aspects. In case of solid tablets or dosage form it typically includes product strength, purity, stability and release. In case of other delivery system it additionally includes some more aspects like in Transdermal patches it must have adhesion property, it must have sterility for parenterals. Product and Process development is guided by this CQA. Considerations for CQA includes:

- Link to the patient
- Safety and efficacy or severity of harm before taking into account risk control
- The rationale to differentiate it from other quality parameters [12]

10.4 Design Space: Design Space is the parameter that provides the information of guarantee of safety. Design Space is basically a way by which one can represent the process understanding that has been or that has to be established. Design Space can be established for any type of process like for unit operation or for multiple operation or for the entire process, that's why it is a multidimensional combination of input variables.

The main benefit of this design space is the cost of establishing it [6].

10.5 Process Analytical Technology (PAT): According to ICH Q8, PAT ensures that the drug product or process remains in an established design space. Process is maintained in an established design space or not, this can be demonstrated by the PAT tools that provides continuous monitoring over a CPP. This is an efficient way to detect failure [13].

Limit flexibility is one of the problem with the design space. So by direct assessment of product quality via this PAT may provide more flexibility and robustness than that of design space [6].

10.6 Critical Process Parameter: Any parameter is said to be a critical if even a minor change in that parameter can lead the drug to fail to meet the QTPP [6]. CPP is basically a process parameter whose inconsistency has an impact on a CQA and must be controlled to meet desired quality of the drug product [14].

10.7 Quality Risk Management: Risk is something that has a chances of occurring of damage and severity of that particular damage. Importance of quality in pharmaceuticals is the first and foremost thing. In case of pharmaceuticals the protection of patient is considered to be as prime objective by managing the risk to quality. The manufacturing, components and use of drug is having a risk of quality [15]. It is very important to make and to maintain the quality of the product throughout its lifecycle. An effective or superior QRM can ensure the product of best quality to patients. If any quality related problem arises then this QRM can improve the decision making.

Principles of quality risk management:

- There should be a assessment of risk of quality and this evaluation must be based on scientific knowledge as it directly deals with life of patients.
- The level of documentation, efforts of QRM must be match with the level of risk [14].

Some of the quality risk management tools are:

- Failure Mode Effects Analysis (FMEA)
- Failure Mode Effects and Critically Analysis (FMECA)
- Fault Tree Analysis
- Hazard Analysis and Critical Control Points (HACCP)

10.7.1 Failure Mode Effects Analysis / Failure Mode Effects and Critically Analysis: It is an inductive method that is used to achieve or determine all the ways a failure of product, system or equipment occur and that's why this method can be applied for all systems, products, equipments and manufacturing process.

The main objective of this analysis is to tell/define all the potential failures so product and process design can eliminate them [15].

FMEA is the most commonly used quality risk management tool, as it is mainly or widely used by the medical practionar. In case of evaluating operation of mechanized system like vial fillings this FMEA can be used [15].

10.7.2 Fault Tree Analysis (FTA): FTA is basically a method that focus on causes or sequence of causes that can potentially results in the failure. Here, there main goal is to know or to reach the root cause of failure. This FTA is good for developing monitoring system. It is useful in the case when attempts to correct the failure or cause of failure been unsuccessful [15].

10.7.3 Hazard Analysis and Critical Control Points: This HACCP tool is mainly used by FDA or mainly used in food industries for certain food producers. This system looks at the entire system and that's why it is more proactive risk management than other systems [14].

It requires less technical information as it deals with the big pictures and identifying and controlling hazards. Their analysis is based on verified flow diagram of process [15].

Overview of Quality Risk Management

12. Applications of QbD

- QbD provides less batch failure.
- Safe and effective and proper use of drug can be assured by this QbD.
- Mainly QbD provides best understanding of process of manufacturing.
- Scientific knowledge of any provided drug or API can be provided by QbD.
- It basically provides better interaction with any industry.
- QbD not only reduces cost but also increases product manufacturing.
- Qbd not only works or focus on drug efficacy but also on patient's safety.

13. Conclusion

Quality by Design is the modern approach that ensures the quality of the product. Th idea of QbD has already uprooted the ongoing industry and in the future it will give successful boost to emerging industries. The main objective of QbD is that it focus on drug efficacy as well as safety

of patients. QbD provides less batch failure and also provides proper use of drug. The major tools of QbD are Target Product Profile, Design of experiment, PAT, Risk assessment tools. QbD provides some of the opportunities like it not only reduces the cost but also increases manufacturing efficiency. ICH guidelines of QbD are Q8, Q9 and Q10. Some of the applications of QbD are like that it provides better interaction with industries and provides scientific knowledge of drug

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