IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
September 2023 Vol.:28, Issue:2

Quality by Design: A Review

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 21 August 2023
Accepted: 23 September 2023
Published: 30 September 2023

Keywords: Quality by design; Quality target product profile; Critical quality attributes; Design space;

ABSTRACT

Quality by design (QbD) is an essential part of the modern advance in pharmaceutical quality. QbD is the best key to building quality in all pharmaceutical products. Under this concept of be throughout design and growth of product, it is important to identify desire product performance report [Target product profile (TPP), Quality Target product profile (QTPP)] and identify critical quality attributes (CQA). To recognize the impact of raw material [critical material attributes (CAM)], critical process parameters (CPP) on the CQAs and identification and control sources of changeability. The plan of pharmaceutical development is to design quality products and its manufacturing process always delivers the future performance of the product. The base of Quality by design is ICH Guidelines Q8 for Pharmaceutical development, Q9 quality risk management, Q10 for pharmaceutical quality systems.

INTRODUCTION

❖ Quality [1,2]

In Quality by Design, Quality is an important word. So Quality is "standard or suitability for the intended use." This term includes such attributes as identity, potency, and purity.

❖ Quality by Design

Pharmaceutical industry is alert on product Quality, Safety, and Efficacy. Product quality has been increasing by implementing scientific tools such as QbD (Quality by Design). Scientific approaches will provide clear and sufficient knowledge from product development to manufacturing. These QbD tools will minimize the risk by increasing the output and quality. Nowadays QbD approach has been successfully implemented in common formulation development. USFDA has released specific QbD guidance for immediate and extended-release drug products as well as biotechnological products. Regulatory authorities are always proposing the implementation of ICH quality guidelines Q8 to Q11 [3].

According to ICH Q8 guidelines, QbD is defined as, " A systematic approach to development that begins with predefined objectives & emphasizes product, process understanding & process control, based on sound science & quality risk management."[4] It means that, design & develop the formulation & manufacturing process to make sure predefined product quality. It requires an understanding of how product & process variables influence product quality. It is a systematic process to build the quality in to final product. QbD requires the identification of all critical quality attributes and process parameters as well as determining the level to which any variation can impact the quality of the final product.

❖ Concepts and Background of QbD [5]

Quality by Design is a concept first outlined by Joseph M. Juran in various publications. He supposed that quality could be planned. The concept of QbD was mentioned in ICH Q8 guidelines, which states that, "To identify quality can not be tested in products, i.e. Quality should be built into product by design." In 1970, Toyota pioneered many QbD concepts to improve their early automobiles, since that time other industry technology, telecommunication & aeronautics have taken this concept & make QbD. In 1990, Medical devices began to show that incorporated many qualities by design aspects. In mid-2002 FDA

published a concept paper on cGMP for the 21st century [6]. These documents expressed a desire that companies build quality, safety, & efficacy in to their new product as early as possible.

❖ The objective of QbD:

➢ The main objective of QbD is to ensure the quality products, for that product & process characteristics important to de- sired performance must be resulting from a combination of prior knowledge & new estimation during development.

➢ From this knowledge & data process measurement & desired attributes may be constructed.

➢ The experimental study would be viewed as positive performance testing of the model ability through Design space.

➢ Ensures a combination of product & process knowledge gained during development.

❖ **Benefits of QbD [7,8]**

For Industry:

➢ Better understanding of the process.

➢ Less Batch failure.

➢ Ensure better design of products with fewer problems in manufacturing.

➢ Allows for continuous improvement in products & manufacturing process.

For FDA:

➢ Enhances scientific base for analysis.

➢ Provide better consistency.

➢ Provide for more flexibility in decision-making.

➢ Ensures decisions are made on science & not on observed information.

❖ **Pharmaceutical Aspects: Traditional vs. QbD Approach [9]**

Advancement in pharmaceutical development & manufacturing by QbD can be explained against the traditional approach as below (Table 1):

Table 1. Pharmaceutical Aspects: Traditional vs. QbD approach.

Aspects	Traditional	QbD
Pharmaceutical Development	Empirical	Systematic, multivariate experiments
Lifecycle management	Post-approval changes needed	Continual improvement enable design space
Mfg. process	Fixed	Adjustable within the design space
Control strategy	Mainly by intermediate product and end product testing	Risk based, Controlled shifted upstream, real-time release
Product Specification	Based on batch data	Based on the desired product performance
Process control	Offline analysis wide or slow response	PAT is utilized for feedback and provide to real-time

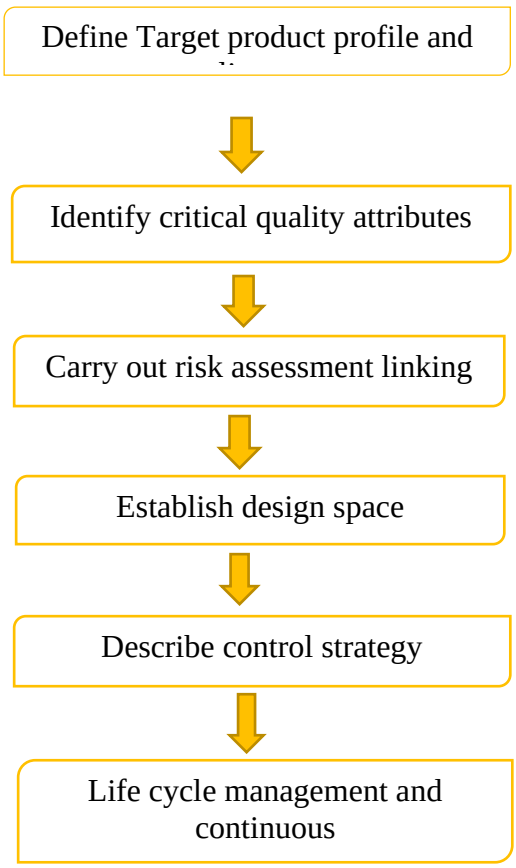

Figure 1. Flow of quality by design

1) In QbD Process, first define the Target Product profile (TPP) & Quality Target Product Profile (QTPP) which describe use, safety & efficacy of the product.

2) Once TPP & QTPP have been identified, the next step is to identify the Critical Quality Attributes. (CQAs).

3) Carry out the risk assessment linking material attributes & process parameters that must be controlled to achieve the desired quality product.

4) After that, confirm the Design space (Figure 2).

5) Implement a control strategy for the entire process using in-process and end-of-process controls.

6) Perform continuous improvement to get consistency in the quality of products.

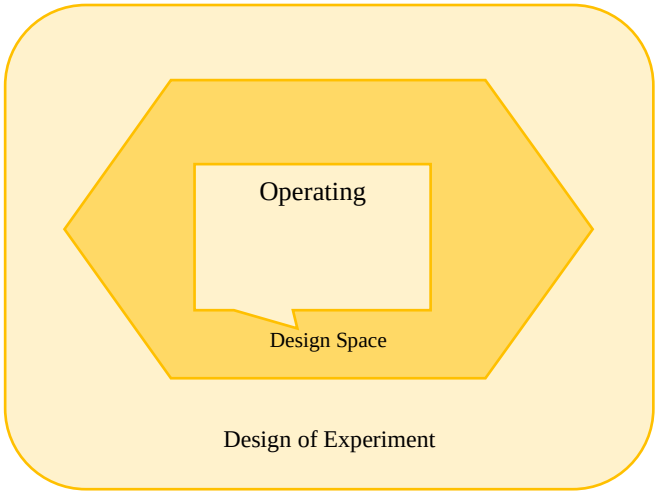

Figure 2. Design space

❖ Target Product Profile (TPP)

Under this title target is an important word. Target is nothing but a result that we try to achieve. So, in this, we target the drug profile or target product which ensures desired quality, safety & efficacy. [10] TPP is defined as, "A prospective summary of the quality characteristics of drug product that ideally will be achieved to ensure the desired quality, taking into account safety & efficacy of drug product."(ICH Q8).

❖ The target product profile should include,

➢ Dosage form

➢ Route of administration

➢ Dosage strength

➢ Pharmacokinetics

➢ Stability

The TPP is a patient & labeling centered concepts, because it identifies the desired performance characteristics of the product, related to the patient's need & it is organized according to the key section in the drug labeling. [11]

Pharmaceutical companies will use the desired labeling information to construct a target product profile.The TPP is then used to design the clinical trials, safety & ADME studies as well as to design the drug product, i.e. The QTPP.

Quality Target Product Profile (QTPP)

QTPP is a quantitative substitute for aspects of scientific safety & efficacy that can be used to design and optimize a formulation and mfg. process. It should include quantitative targets for impurities, stability and product-specific performance requirements. QTPP is not specification because it includes tests such as bioequivalence or stability that are not carried out in batch-to-batch release. QTPP should only include patient-relevant product performance. [10]

The Quality Target product profile is a term that is an ordinary addition of TPP for product quality. It guides formulation scientists to establish formulation strategies and keep formulation is well-organized. QTPP is related to identity, assay, dosage,form, purity, and stability in the label.[5]

Critical Quality Attributes (CQAs)

A CQA has been defined as “a physical, chemical, biological or microbiological property or characteristics 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 ICHQ9. Critical Quality Attributes are generally associated with the drug substance, excipients, intermediates and drug product. Critical Quality attributes include the properties that impart the desired quality, safety, and efficacy. CQAs for biotechnological products are typically those aspects affecting product purity, and stability. Drug product CQAs can be identified from the Target product profile. Use of strong risk estimation methods for the identification of CQAs is new to the QbD standard.

Risk Assessment [11]

Risk assessment is the linkages between material attributes & process parameters. It is performed during the lifecycle of the product to identify the critical material attributes & critical process parameters.

MATERIAL ATTRIBUTES

A material attributes can be an excipient raw material, drug substances, reagents, solvents, packaging & labeling materials.

Material attributes can be quantified & typically fixed but sometimes can be changed during further processing.

E.g. Impurity profile, porosity, specific volume, sterility.

Quality risk assessment

➢ The evaluation of the risk to quality should be based on scientific knowledge & it provides safety to the patient.

➢ Describes systematic processes for the assessment, control, communication & review of quality risks.

➢ Applies over the product lifecycle, development, manufacturing & distribution.

Critical material attributes (CMA) and critical process parameters criticality (CPP)

• A material attribute is critical when a practical change in that attribute can significantly impact the quality of the output material.

• A process parameter is critical when it has a high impact on critical quality attributes.

• CPPs are responsible for ensuring the CQAs & it is identified from a list of potential CPPs using risk assessment.

Three categories for attributes or parameters -

➢ Unclassified parameters: The criticality of unclassified parameters is undetermined or unknown. The additional data are needed to classify an unclassified parameter as critical or non-critical.

➢ Critical parameters: A parameter is critical when a realistic change in that parameter can cause the product to fail to get the QTPP.

➢ Non-critical parameter: No failure in QTPP observed in the potential operating space & no interactions with other parametersin the established suitable range.

Examples for CPP are temperature, addition rate, cooling rate, rotation speed, pH, agitation, and dissolved oxygen.

A design space

Design space is defined as, a "Multidimensional combination and interaction of input variables (e.g. material attributes and process parameters) that have been demonstrated to provide assurance of quality."

The linkage between the process inputs and critical quality attributes can be described in the design space. A design space is a way to represent the process understanding that has been established.

It is proposed by Applicant and reviewed by the controller. In a typical design space approach a sponsor identifies the unclassified parameters and then does a DOE on some of the unclassified parameters with the other unclassified parameter. Analysis of historical data can provide the basis for establishing a design space. How a design is developed, it is expected that operation within the design space will result in a product meeting the defined quality attributes. Once design space is accepted, then regulatory post-approval change requirements will be simplified inside space. When you define your design space, then you are able to plan how to control the process.

CONTROL STRATEGY

Control strategy is defined as, "A designed set of control, derived from current product and process understanding that assures process performance and product quality." A control strategy is designed to ensure that products of required quality will be produced consistently. Once sufficient level of process understanding is achieved, a control strategy should be developed that assures the process will remain in control within normal variation in material attributes & process operating ranges.

A control strategy may include input material controls, process controls, and monitoring, design spaces around individual or multiple unit operations, and final product specifications used to ensure consistent quality.

Elements of a Control Strategy

• Procedural controls

• In-process controls

• batch release testing

• Process monitoring

• Characterization testing

• Comparability testing

• Constancy testing

The control strategy in the QbD standard is established via risk assessment that takes into account the criticality of the CQAs.

IFM (Impurity Fate Mapping) - Is an example in which raw material & process impurity sources are identified & their fate mapped throughout the process. Remove impurity is an essential element of control strategy.

Product Lifecycle Management & Continual Improvement

Throughout the product lifecycle, companies have opportunities to evaluate modern approaches to improve product quality. After approval, CQAs would be monitored to ensure that the process is performing within the defined suitable variability that served as the basis for the filed process design space. The primary benefit of an extended process design space would be a more flexible approach by regulatory agencies. Therefore, process improvements during the product life cycle with regard to process consistency. [6]

Application of QbD to Influenza Vaccines

Influenza vaccine:

Influenza (flu) is caused by influenza viruses & is spread mainly by coughing, sneezing, & close contact with infected persons.

Flu is a communicable disease that spreads around the US every winter in Oct.

Symptoms:

• Fever/chills

• Sore throat

• Muscle aches

• Fatigue

• Cough

• Headache

Vaccination

Vaccination is the phenomenon of protective immunization. In the modern concept vaccination involves the administration (injection or oral) of an antigen to obtain an antibody response that will protect the organism against future infections. [8] Attenuated viruses are genetically modified pathogenic organisms that are made nonpathogenic &used as vaccines. Attenuated strains of some pathogenic organisms were prepared by prolonged cultivation for weeks, months or years. Due to this, the infectious organism would lose its ability to cause disease but retains its capacity to act as an immunizing agent. Flu vaccine is the best protection against flu & its complications. Flu vaccine also helps to prevent spreading flu from person to person. Flu vaccine can not prevent all cases of flu but it is the best protection against acute respiratory diseases. Some people should not get this vaccine-

1) If they have any severe, life-threatening allergies. E.g.: Allergy to gelatin, antibiotics or eggs, you may be not to get vaccinated.

2) If you are not feeling well, then also not to get vaccinated.

Cell-Culture Based Influenza Vaccine Production [12]

Objectives

1) Modern cell-culture technology potentially allows for quick, efficient production.

2) Production of cell-derived vaccine requires little advanced planning & many provide response in the event of virus.

Influenza vaccine production process involves 5 fundamental steps:

1) Cell propagation/Preparation of substrate.

2) Virus propagation

3) Purification

4) Inaction & Splitting

5) Blending, Filling, & Approval.

1) Cell propagation/Preparation of substrate: Take the frozen, preserved cell culture from WBC cell line & grow in an incubator at 37°c. Then these cells are first grown in small volume of culture medium, due to this cells are grown & multiply. Then transfer in to succively larger container.

2) Virus propagation: Once a high number of cells have been produced, add influenza seed virus obtained from WHO diagnostic laboratory in to cell containg bioreactor (Fermenter) where virus infects the cells & multiplies & produce more virus particles. After several days viruses destroyed the cell in bioreactors. The virus is harvested by removing the waste made by the cells and made non infectious.

3) Purification: Using a centrifuge or chromatography, the virus is then separated from the cells and removed from the solution.

4) Inactivation and splitting: A chemical process is used to inactivate the virus, stripping it of its ability to infect, for that formaldehyde is used, this is called as splitting. Then the surface antigen is separated and extracted from the virus.

5) Blending, filling and approval: The noninfectious solution is blended, concentrated and filled into a sterile syringe.

By using QbD the following parameters should be controlled during vaccine production process [8].

1) Cell propagation: In this step, limiting the concentration of nutrients may be helpful for optimal cell growth. If high nutrient concentration, then it inhibit cell growth. For that to do on line monitoring of the nutrient concentration.

2) Virus prorogation: The following variable parameters controlled during fermentation process.

• pH: for maximum effectiveness of fermentation can be achieved by continuous monitoring pH i.e. It required the most favorable pH.

• Temperature: Temperature control is important for good fermentation process. If the temperature is lower than it causes reduced product formation & if it is higher then it affects the growth of organisms. To avoid this, bioreactors equipped with a heating & cooling system as per the requirement to maintain the reaction vessel at optimal temperature.

• Dissolved oxygen: Optimal supply of nutrients & oxygen, due to this it prevents the growth of toxic metabolic byproducts.

• Agitation: Good mixing also creates a favorable environment for growth & good product formation. If agitation is excessive then it damages the cells & increases temperature of the medium.

• Foam formation: Avoiding this parameter antifoam chemicals are used such as mineral oils, vegetable oils which lower the surface tension of the medium & cause foam bubbles to collapse. Also mechanical foam control devices fitted at top of fermenter.

3) Purication: in this step check the purity by using ion exchange chromatography & remove the impurity.

4) Inactivation: Optimum concentration of formaldehyde is used for the inactivation of viruses.

REFERENCES

1. Gillian Doherty and Jane Beach Martha Friendlyn “Quality by design: What do we know about quality in early learning and child care, and what do we think?” A literature review pp. 1-32.
2. ICH Q8 (R2) (2009) Pharmaceutical Development.
3. Lawrence X. Yu (2006) Director of Science. “Implementation of Quality by Design”, Question based review.

4. Anat IB (2013) QbD Strategy Leader, "Bud implementation in Generic Industry: Overview and Case-Study" IFPAC JAN.
5. Avellant J (2008) "Why Quality by Design?" Expert Brefings pp. 1-12.
6. Roy S (2012) "Quality by Design-Holistic concept of concept of building quality in pharmaceuticals". Int J Pham Biomed Res 3: 100-108.
7. Blackburn TD (2011) "An Introduction to QbD (Quality by Design) and Implications for Technical Professionals", ISPE CASA Annual Technology Show.
8. Satyanarayana U "A text book of Biotechnology". p. 513.
9. Nishendu P et al. (2012) "A complete review of Quality by Design". Int J Pharm Sci Rev Res 17:20-28.
10. Lawrence X. Yu (2008) "Quality by Design: Concept for ANDA's".AAPS J 10: 268-276.
11. ICH Q9: Quality Risk Management - an update 14 May 2014.
12. Arvydas A et al. (2009) A novel mammalian cell-culture technique for consistent production of influenza virus vaccine. In Vaccine 27: 6022-6029.
13. A-VAX case study: Applying Quality by Design to vaccines.
14. Dama GY (2010) Simultaneous Estimation of Ramipril and Enalapril by Using HPTLC. International Journal of Universal Pharmacy and Life Sciences 1: 1-10.