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Review Article

A REVIEW ON QUALITY BY DESIGN (QbD) APPROACH IN PHARMACEUTICAL DRUG DEVELOPMENT

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A novel idea called Quality by Design (QbD) has been developed to improve the quality of pharmaceutical goods. It is a crucial component of the contemporary strategy for pharmaceutical quality, notwithstanding inherent process and material variability. Although QbD is the greatest means to ensure quality in all pharmaceutical goods, it also presents a significant barrier for the sector because its processes are set in stone. It is crucial to specify the desired product presentation profile [Target Product Profile (TPP), Target Product Quality Profile (TPQP)] and identify key quality attributes (CQA) within this idea of QbD during the creation and growth of a product. An emerging concept called QbD provides pharmaceutical manufacturers with better self-regulated flexibility. The article discusses the pharmaceutical QbD technique and how it may be used to the development of the pharmaceutical product in the context of drug development.

Key words: Quality by Design (QbD) ;Target product Quality Profile (TPQP);Critical Quality Attributes(CQAs); Pharmaceutical quality by design; process understanding; Design space

INTRODUCTION

The idea of Quality by Design was created by Dr. Joseph M. Juran, a quality pioneer (QbD). According to Dr. Juran, a product's quality should be taken into account, and the majority of quality crises and issues are related to the initial design process's methodology. 1 A produced good free of contamination and dependably delivering the therapeutic advantage claimed in the mark to the user is what Woodcock defines as "a high-quality drug product." Risk-based approaches and QbD morality approval are encouraged in the regulation of pharmaceutical products by the US Food and Drug Administration (FDA). With the recall that demonstrated that increased testing does not necessarily result in greater product quality, FDA's focus on QbD first gained traction. Addiction to the brand must be created via quality.[2]

A methodical approach to development that starts with a predetermined goal and stresses process control, product and process support, and value risk management is known as this. Pharmaceutical firms are well-versed in product efficacy, safety, and quality, which is particularly crucial. The calibre of the goods has improved QbD (Quality by Design).[3]

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The data required for product development is provided via a fact-based method. These QbD devices will lower exposure while reducing output and quality. The QbD technique has been effectively used in the creation of regular formulations. Specific QbD recommendations for the immediate and complete release of pharmaceutical and biotechnological products have been published by the USFDA. Regulatory authorities constantly advocate for the fulfilment of ICH quality standards like.

ICHQ8= Pharmaceutical Development

ICHQ9= Quality Risk Management

ICHQ10= Pharmaceutical Quality System

ICHQ11= Development & Manufacture of Substance

Pharmaceutical Quality by Design Objectives

1. One of the main goals of QbD is to guarantee the quality of products, for that product and process characteristics are vital for presenting desires, they must be the result of a mixture of prior information and novel estimation during development.
2. It is possible to construct this knowledge and statistics process, measurement & desired features.
3. This makes sure that knowledge acquired during development of both products and processes is combined.
4. To achieve significant product quality, but that is based on clinical concert.
5. To improve process qualifications and reduce product variability and defects by enhancing product and process design understanding and manage.
6. To increase productivity in product development and production.
7. To create post-approval change management and root cause analysis.[4]

Figure No. 1 FDA-View-On-Quality-by-Design-in-pharmaceuticals[6]

Advantages of QbD

8. More effective and well-organized control of changes.
9. Investment returns and cost savings.
10. In case of variations in conditions, the developed method will be extra robust which

gives higher level of confidence.

11. It helps to escalate understanding of the method.

12. This approach proposed superior transfer achievement when method is transferred from research level to quality control department.

13. Design space concepts avoid post-approval amendments that could force any enterprise to pay a high price for any of the firm.

14. It provides a space an area for invention of latest techniques by continuous improvement during life cycle.

Additional opportunities:

15. An enhanced QbD approach to pharmaceutical development provides opportunities for more flexible regulatory methods. Ex: Modifications to manufacturing made without additional regulatory assessment within the allowed design space.

16. A reduction in submissions for post-approval.

17. When procedures are outstanding in the design space, it can be possible to improve them without resubmitting them to the FDA, which leads to better innovation.

- A greater transfer of advanced technology to manufacturing.
- Higher regulator assurance of robust products.
- Risk-based approach and detection.
- Improved, yields, lower price, less investigations, lower testing, etc.
- Time to market reductions, which were achieved, among others, from 12 to 6 years.
- First time right: lean possessions management.
- Continuous improvement over the total products life cycle (i.e. controlled ,patient guided variability).

QbD activities within FDA

The application of QbD is guided by the following steps:

Based on the submission of the product and comprehension of the procedure, the FDA's "Office of New Drug Quality Assessment (ONDQA)" recognised a new risk-based "pharmaceutical quality assessment system (PQAS)". Pharmaceutical companies can gather data for a new medicine application by implementing a conduct programme that demonstrates the application of QbD concepts, product expertise, and process understanding. Januvia from Merck & Co. was the first product to be authorised on the basis of such an application in 2006.

A Question-based Review (QbR) Process has been introduced at the Office of Generic Common Drugs of CDER. By enhancing pre-approval inspection procedures to evaluate the likelihood of commercial processes and

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determine whether a state of process control is maintained throughout the lifecycle in accordance with the ICH Q10 lifecycle Quality System, the Office of Compliance at CDER has contributed to the QbD plan. The first QbD approval for a biologic licence application (BLA) with design space has been given to Gazyva. Although it is acknowledged that QbD would offer better design predictions, industrial manufacture and upgrade expertise also teach about the process and the raw materials used.[2,3&5]

ICH activities

Together with authorities in the European Union (the European Medicines Agency) and Japan, the FDA has supported quality by design principles through the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. These coordinated concepts are included in the ICH Guidelines Q8 through Q11, which assist manufacturers in incorporating quality by design into their procedures. The development of drug formulations based on QbD is described in the 2004 edition of ICH Guideline Q8—Q8(R2). The ICH Guidelines Q9, Q10, and Q11 all provide descriptions of quality risk management plans, pharmaceutical quality systems, and the development of active pharmaceutical ingredients, including biologicals.

In response to the recommendation for the Product Lifecycle administration Plan that was first made clear in the Guideline Q10, the ICH produced Guideline Q12 in November 2017 for public comment. The ICH states that Guideline Q2 (Analytical Validation) will be updated and expanded into the instructions Q2 (R2)/Q14 to incorporate Analytical quality by design, or AQbD, while Guideline Q13 will maintain the prior guidelines to enable ongoing pharmaceutical industrialization.

The ICH Steering Committee meets twice year to go over the progress of its initiatives. Making sure that quality risk management and knowledge management are used should make it simpler to make lifecycle adjustments that maintain process control and product quality. [12]

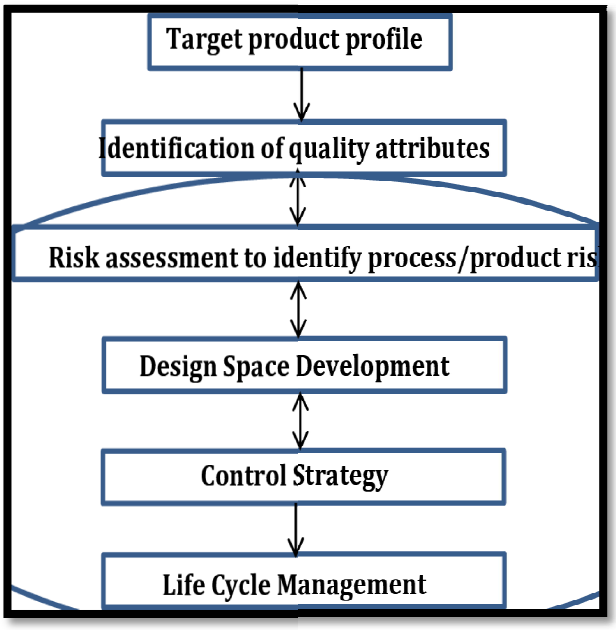

Figure No 2: The QbD process for creating a pharmaceutical product.[8]

Application of QbD or elements of QbD to analytical method

1. In determination of contamination.

2. In screening showing of column used for chromatography

3. In development of HPLC method for drug products/substances

4. In stability studies In UHPLC

Elements of QbD

Quality Target Product Profile (QTPP) That Identifies The Critical Quality Attributes (CQA) Of The Drug Product: - The qualities of a drug product that should be attained to ensure the desired quality, while also taking into account the drug product's safety and efficacy, are likely summarised as an intended use in a QTPP. The Chemistry, Manufacturing, and Controls (CMC) side of product development is the primary focus of the Quality Target Product Profile (QTPP), a subset of the Target Product Profile (TPP). The product improvement is produced by QTPP. The following variables could be considered for the QTPP:

- The clinical environment, the administration route, the dosage forms, and the delivery methods.
- Therapeutic moiety release or delivery

properties that are appropriate for the dosage form of the medication product being created and affect pharmacokinetic variables (such as dissolution and aerodynamic performance).

- Drug product quality criteria (eg. sterility,

purity, stability, and drug release) appropriate for the intended marketed product [5].

Identification of the CQAs of the drug product is the next step in drug product development: A CQA is a physical, chemical, biological, or microbiological quality or feature that should fall within a certain range or distribution in an output material, particularly a completed pharmacological product. Along with identification, assay, content uniformity, degradation products, residual solvents, drug release or dissolution, moisture content, and microbiological limitations, a drug product's quality attributes may also comprise physical traits including colour, shape, size, odour, score configuration, and friability. These characteristics might be unstable or harmful. When assessing an attribute, it is important to keep in mind how much the patient might be harmed if the product is found to fall outside of the acceptable range for that attribute.

It should go without saying that before beginning any development work on a new product, it must be adequately defined. However, it is commonly forgotten that the target features of the medicinal product must be specified beforehand. As a result of the lack of a clearly defined QTPP, considerable time and resources have been wasted. The importance of accurately defining the QTPP before doing any development, the author writes, is demonstrated by recent research from Raw.[5,11]

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Product Design and Understanding:- - The ICH Q8 (R2) advice states that the process design, understanding, and control have been the focus of QbD. The importance of product design, understanding, and control must be made evident. Product design determines whether a product can meet patient needs, and this decision is supported by additional clinical research. Stability studies, which are used to support this, demonstrate that product design has an impact on whether a product can continue to function over the course of its shelf life.[3]

To create a quality product that can deliver the estimated QTPP for the course of the product's shelf life is the main goal of product design and understanding. Designing a product is an open-ended process with several design options. The following are important components of product design and understanding:

1. Drug substances are classified as physical, chemical, and biological substances (s).

2. Determining and choosing the right excipient kind and grade, as well as being aware of the inherent excipient variability

3. Drug and excipient interactions.

4. Drug formulation optimization and excipient and drug substance CMA identification.

To design and produce a potent therapeutic product with the desired CQAs, a product development scientist must consider the physical, chemical, and biological characteristics of the medication ingredient carefully. A physical asset's physical description, polymorphism and form transition, and water solubility as a function of pH, inherent dissolving rate, hygroscopicity, and melting point are all examples of physical attributes. Particle size distribution and form are both included in the physical description. For instance, the possible impact of pharmaceutical solid polymorphism on solubility, dissolution, stability, and manufactureability has attracted a lot of attention recently. Chemical properties include PKa, chemical stability in the solid state and in solution, as well as photolytic and oxidative stability. Examples of biological properties include membrane permeability, bioavailability, and partition coefficient.

1. Excipients used in pharmaceuticals are parts of a drug product that aren't the active medicinal ingredient.

2. Support the manufacturing process for the dosage form when processing it.

3. Ensure stability, bioavailability, or patient acceptability are maintained, supported, or improved.

4. Assist in helping to identify the product.

5. Improve any other aspect of the drug's overall safety, efficiency, or delivery while being stored or used.

They are defined by the roles they perform in pharmacological dosage form. Some of the 42

functional excipient categories listed in USP/NF include binders, disintegrants, fillers (diluents), lubricants, glidants (flow enhancers), compression aids, colours, sweeteners, preservatives, suspending/dispersing agents, pH modifiers/buffers, tonicity agents, film formers/coatings, flavours, and printing inks.

Excipients, as is widely known, can be a significant source of variability. Despite the fact that excipients can affect the stability, manufacturability, and bioavailability of pharmaceuticals, they are frequently chosen ad hoc without a formal drug-excipient compatibility test. ICH Q8 (R2) recommends drug-excipient compatibility studies to aid in the early prediction of compatibility in order to avoid costly material waste and delays. The following are some of the benefits of conducting systematic drug-excipient compatibility studies:

1. Reducing unplanned stability failures, which typically result in longer development times and higher costs.

2. Reducing a formulation's stability, and therefore the drug product's shelf life.

3. Enhancing knowledge of drug-excipient interactions that can aid in determining the root cause of a problem, should one develop.

Formulation optimization research is critical for developing a powerful formulation that will not fail. Without optimization studies, a formulation is more likely to be high risk since it is uncertain if any modifications to the formulation itself or the qualities of the raw materials will drastically impact the value and performance of the drug product, as evidenced in recent examples. Formulation optimization studies provide important information on the following topics:

1. Identification of CMAs of the drug ingredient, excipients, and in-process materials.

2. Robustness of the formulation, including the development of functional linkages between CQAs and CMAs.

3. The creation of drug substance and excipient control techniques.

In a QbD strategy, what matters most is not the quantity of optimization studies carried out, but rather the relevance of the research and the usefulness of the information learned for creating high-quality pharmaceutical products. Therefore, the QbD is not the same as design of experiments (DoE), but the latter may be a significant part of the QbD.

Excipients, in-process ingredients, and drug substance all have a variety of CMAs. To assure the intended quality of the drug ingredient, excipient, or in-process material, a CMA is a physical, chemical, biological, or microbiological element or characteristic of an input material that should be within an appropriate range or distribution.

Because there are numerous characteristics of the drug substance and excipients that may

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potentially affect the CQAs of the intermediates and finished drug product, it is unrealistic to expect a formulation scientist to investigate every identified material attribute during formulation optimization studies. As a result, a risk assessment would be useful in selecting which material features should be researched further. The judgement should be based on broad factual information as well as the formulator's experience. The material attribute is regarded critical when a logical change in a material feature has the potential to significantly alter the value of the output material. Understanding products necessitates the ability to link input CMAs with output CQAs.

The following are some possible approaches to gain product understanding:

1. List all characteristics of the known input materials that can impair the creation's performance.

2. Use risk assessment and understanding of the facts to spot potentially dangerous characteristics.

3. Define thresholds or ranges for certain potentially dangerous material characteristics.

4. Plan and carry out tests, utilizing DoE as necessary.

5. Examine the experimental results and, if practical, use first-principles models to ascertain whether a characteristic is essential.[11&14]

Quality risk management (QRM) FDA defines: - As it assists in determining the level of the impact of critical material characteristics (CMA) and critical process parameter (CPP) on CQAs, QRM is a crucial component of QbD and can help prioritize the CQAs. In complicated processes, particularly those involving biologics or bio-similar, they play a crucial role.

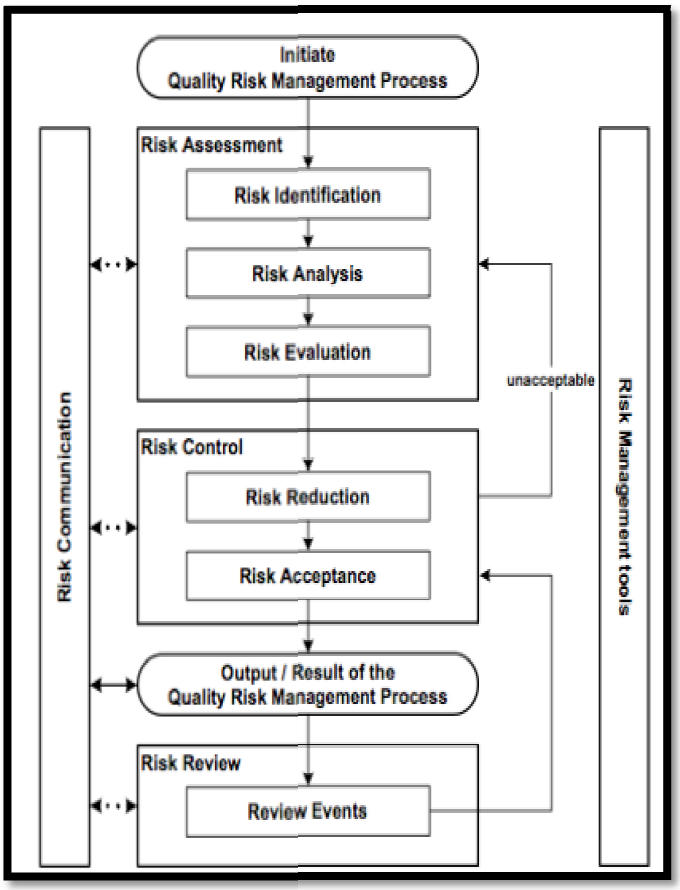

Figure No. 3 Overview of Quality Risk Assessment[16]

Design space :- A design space is a multidimensional set of input variables that have been proved to give attribute certainty, such as material properties, their relationships, and process parameters. A design space can be built for a single unit, many unit operations, or

the full process. Although creating the design space is optional in accordance with FDA protocol because understanding of the product and process can be established without a formal design space, such an approach can help to improve understanding and achieve system-wide control.

The one-factor-at-a-time (OFAT) strategy, which varies only one factor or variable at a time while keeping the other variables constant, can be used in this case. When examining two or more components, designs of experiment (DoE) approaches that modify a number of variables simultaneously are more effective. Factorial designs (full or fractional) and the response surface methodology (RSM) are characteristic tools for this kind of application. The key advantages of using DOE approach are summarized as following:

1. Detailed data from the fewest possible experiments.

2. Examine effects one at a time by altering each operating parameter simultaneously.

3. Is able to take into consideration

experiment, process, material, or operator variability.

4. The ability to demonstrate how each variable interacts with the others. Basic steps involved in DoE approach are as follows:-

5. Defining input & output variables and range

6. Select appropriate experiment design & perform the run

7. Model diagnostic

8. Illustration of design space

[A]. **Defining input and output variables and range:** The input variables and their ranges can be defined based on prior knowledge and risk assessment. You can also use a screening design, such as a complete or fractional factorial design, to determine the range of different variables. A CQA or anything similar should be the response variable.

[B]. **Select appropriate experiment design and perform the run:** The goal of the research (such as a screening, optimization, or robustness study), the factors and interactions involved in the research, and the resources available (such as literature knowledge, time, labor, cost and materials) can all influence the choice of experimental design.

[C]. **Model diagnostic:** The first thing to do after getting the initial model is to make sure its accurate. Typically, the ANOVA method is used to confirm a parameter significance. If a models residuals have a normal, independent distribution, a zero mean, and a constant variance, it is said to be “excellent fit”. The normal probability plot of residual, residuals plotted against anticipated values, and residual plotted against experiment run order can all be used to study this distribution.[9,13]

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[D]. **Illustration of design space:** There are various ways to tabulate or graphically depict the design space. The following provide graphic examples of the design space:

a. Contour plots: A contour plot is a two-dimensional graph that shows the relationships between three numerical variables. Three variables are used: two for the X and Y axes, and one for the contour levels Z. To improve the quality and performance of contouring, you can interactively locate, name, colour, and shift contour levels as well as alter the resolution of rectangular grids.

b. Three-dimensional plots: These plots are employed to demonstrate and investigate the simultaneous impact of two input factors on an output variable. These plots are excellent for exhibiting the process shape, however contour plots are better suited for identifying or displaying the process parameter operating ranges.

c. Overlay plots: The usage of overlay plots is flexible when there is more than one quality rating in the design space. The design space is displayed in the overlay window and illustrates the various combinations of the variables that will produce outcomes within the acceptable range. According to the FDA, a regulatory application pertaining to design space should cover the following topics:

1. A description of the design space with key and other pertinent parameters.

2. Ranges of material inputs and process parameters, graphic representations (contour, interaction, or overlay plots), or more intricate mathematical relationships can all be used to depict the design space. the link between the CQAs and the interactions of different input factors (such material qualities and/or process parameters). These connections can be shown using interaction graphs.

3. Evidence for the design space's rationale, such as but not limited to historical knowledge base, QRM findings, and experimental investigations.

4. The interaction between other unit operating phases and the suggested design space.

5. The findings and recommendations of any research done on a design space at various scales.

6. Evidence that the control method guarantees that the production process is kept within the limits.[16]

[6] **Control Strategy:** A control strategy is defined as "a planned set of controls generated from existing product and process information that ensures process performance and product quality." Design Space, process controls, and requirements are all part of the Quality Control Strategy. As a manufacturer acquires experience, their approach adapts to their present degree of process expertise. Initial

measures, controls, or models may be updated or deleted, or it may be recognised that further controls are required. Other changes to the control strategy may be related to ongoing advancements, such as the use of better analyzer or control technologies. In light of new product and process knowledge, corrective and preventive actions should be performed, and the Control Strategy should be modified as needed (including any regulatory actions required) To apply process analytical technology (PAT) in the Control Strategy, process models (multivariate prediction models) that anticipate CQAs, CPPs, or a combination of the two will be required. These models may also require regular updates, depending on the model's maturity (e.g., quantity). A generic sponsor employs a control technique to ensure consistent quality while scaling up their technology from the exhibit batch given in the ANDA to commercial production. Every process presently has a control strategy. (3,12) A manufacturer is also prohibited from changing any other process variables or operating parameters (a significant number of UPPs) listed in the batch record without first submitting supplements to the FDA.

[7] **Product life cycle:** In the QbD paradigm,

process changes within the design space will not require review. As a result, with fewer post-approval submissions, process improvements in terms of consistency and throughput might be made across the product life cycle. A better understanding of the manufacturing process would enable more informed risk assessment in accordance with ICH Q9 about the effects of process changes and manufacturing deviations (excursions) on product value in addition to regulatory flexibility. [11,15,14]

Quality by Design Tools

The tools for the QbD process include design of experiments (DOE), risk assessment, and process analytical technology (PAT).

[A] **Design Of Experiment (DOE):-** DOE structured, organized method for determining the relationship between factors affecting a process and the response of that method, DOE Methodology.

The DOE also establishes relationships between input factors and output outcomes. A set of controlled tests are established in which intended modifications to the input are made. The effect of these adjustments on a predefined output is then evaluated. DOE's advantage over the traditional univariate approach of development study is its capacity to precisely pinpoint how various elements interact to affect the reactions to the outputs. DOE is critical as a formal method of maximising information while minimising the amount of resources required. DOE studies can be combined with mechanism-based investigations to improve product and procedure understanding.[5]

[B] **Risk Assessment :-** Risk is defined as the

mix of the likelihood of damage occurring and the degree of that harm. Risk assessment refers to the systematic process of obtaining data in order to make a risk judgement within the context of a risk management strategy. It entails identifying hazards as well as investigating and assessing the dangers associated with exposure to such risks.

[C] **Process Analytical Technology (PAT):-** A system for designing, analyzing, and control manufacturing through timely measurement (i.e. during processing) of critical quality and performance attributes of raw and in process materials and processes with the goal of ensuring final creation value. In PAT, the term "analytical" is used generically to refer to integrated chemical, physical, microbiological, mathematical, and risk analysis.

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