



QUALITY BY DESIGN IMPLEMENTATION IN THE DEVELOPMENT OF DERMATOLOGICAL MEDICINAL PRODUCTS

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Abstract: The Quality by Design (QbD) methodology has recently been used in the creation of pharmaceutical formulations. Modern and reliable quality by design indicates that structure plays a key role in the process of getting drugs of high quality. QbD approach guarantees security, adequacy and nature of item with an undeniable degree of efficiency.

Executing into practice the QbD to effective topical dose structures underlying phases. Incorporating QbD methodologies involves creating a quality target product profile (QTPP) and selecting crucial quality attributes (QAs) to develop a plan for a quality-based, non-exclusive, beneficial dermatological product. Characterizing the quality target product profile (QTPP), a list of quality attributes (QAs) that are intended to be present in the finished product, is the first stage in developing an item using this effective process.

The limitations of the assembling approach as well as the fixes used have an impact on these quality attributes. Therefore, it is necessary to indicate critical material attributes (CMAs) and critical process parameters (CPPs). It is deliberate, pragmatic and hazard-based approach in drug improvement. Administrative specialists overall additionally support the transformation & Quality by Configuration execution methodology in drug advancement. QbD apparatuses like plan of trial, hazard appraisal, and interaction scientific innovation help to lay out a control procedure for each medication item with a choice of ceaseless observing and improvement for a quality drug product. The purpose of this brief review is to explain how pharmaceutical Quality by Design is perceived.

Index Terms - Quality by design (QbD), quality target product profile (QTPP), critical material ascribes (CMAs), critical process parameters (CPPs), quality attributes (QAs), Degree of efficiency

I. INTRODUCTION

Quality by design is a part of the modern approach to pharmaceutical quality. Joseph M. Juran was the first to describe QbD, and it has been widely used, especially in the automotive sector [Vrushali e.al., 2016]. To find the optimal solution, Quality by Design (QbD) based Design of Experiment (DoE) provides a holistic picture of the product and processes [Singh et al., 2011]. QbD is described as "An organized method of development that begins with established goals and emphasizes product and process understanding along with process robust science and effective risk management under control in ICH Q8 (R2)" [Q8(R2) – ICH,2009] [Daisy et. al.,2019].

Due to its advantages in ensuring high quality drug products without requiring considerable regulatory control, the QbD idea has drawn increasing attention in the production of new pharmaceuticals [Rathore, 2009]. The International Conference on Harmonization (ICH) Q8 guideline defines QbD as an organized strategy for drug discovery that begins with established objectives and emphasizes knowledge of products

and processes along with oversight, based on sound investigation and management of quality risks. [Ana et. al.,2018] Quality by Design (QbD) is a concept that has been supported by international regulatory organizations like the European Medicine Agency (EMA) and the United States Food and Drug Administration (US FDA) as a way to gain a thorough understanding of the way pharmaceuticals are produced at various stages of the initial medication creation procedure and the commercialization session. [Nicole et. al.,2019].

One key method for ensuring topical semisolid solutions operate as expected is quality assurance. Skin morphology and bio-physiology fluctuate significantly between people and among various body areas. [Igarashi et. al., 2007]. As a result, it is essential for goods that need to exert their effects on the skin to make an inherent claim about specific quality attributes (QAs). Quality must be incorporated into the product. [Sarika et. al., 2020]

II. PHYSIOLOGY OF SKIN

The skin is massive and most prominent organ of the human body, acting as an effective barrier between the body and the outside world to prevent the passage of harmful substances. It also serves an important sensory function. The stratum corneum (SC) (nonviable epidermis), the viable epidermis, the dermis, and the subcutaneous tissues (hypodermis) make up its four distinct parts. Skin structure also includes appendages like sweat glands and hair follicles connected to sebaceous glands. [Ana et. al., 2018][Walters and Brain, 2004]

Among the various dermatological medication forms on the market, cream formulations continue to draw more attention as effective ways to penetrate the skin with medications and cosmetics. These are referred to as biphasic systems, which are interesting formulations for delivering both hydrophilic and lipophilic medicines. They are composed of two immiscible liquids, one of which is uniformly disseminated throughout the other to create oil-in-water (o/w) or water-in-oil (w/o) emulsions. [Ana et. al., 2019] Skin penetration (both rate and extent) is preferred for medications that use topical distribution to reach systemic circulation (i.e., transdermal) for their therapeutic impact. Topical dermatologic drugs, in contrast, need to stay either on or in the upper layers of the skin to exercise their therapeutic action and reduce penetration outside of the target skin layer or lesion. [Vinod et. al.,1992][Luke et. al.,2020]

The epidermal' topmost layer, the stratum corneum, is made up of layers of dead corneocytes that vanished as fresh outer layer of corneocytes develops. The primary emphasis IVPT (In Vitro Release Testing) is the skin layer which acts as the biggest barrier to dermal absorption. After being surgically removed from the body, the stratum corneum maintains its durability and, along with the epidermis, serves as the practical membrane for assessing the penetration speed of a test component. Important things to take into account when choosing and getting a skin membrane ready for the IVPT (In Vitro Release Testing). [Luke et. al., 2020] The greatest and most important barrier for molecular diffusion through the skin is the SC, which is the epidermis' outermost layer. Drug release from the dosage form is the first step in the permeation process, which followed by diffusion into and through the SC [Ana et. al., 2018].

III. PHARMACEUTICAL QUALITY BY DESIGN

In the pharmaceutical industry, "QbD" refers to a combination of methodical and planned steps taken to achieve a specific goal. The objectives of QbD approach are:

- Achieving a suitable product quality based on clinical experiences and performance data
- Enhancing process manufacturing by reducing inconsistency and flaws thereby improvising its product design, comprehension, and management of processes.
- To develop the manufacturing efficiencies to augment product development
- To carry out root cause analysis and to build up management protocols for post-approval needs [Manish et. al.,2020]

The FDA launched a new project in 2002 called Pharmaceutical Current Good Manufacturing Practises for the 21st Century to encourage the pharmaceutical sector to adopt cutting-edge quality management practices based on QbD. [Osborne, 2016] The core principle of According to QbD, quality must be incorporated into the formulation before it is tested. [Sivaraman,2015][Sarika et. al., 2020] The main goals of QbD are to decrease product variation, increase process efficiency, and lower costs throughout the process. Organized research and development accelerates the product's entry into the market and improves the quality process. [Weinberg,2010] Designing the target for the intended product profile and defining the quality target product profile (QTPP) are the first steps in the QbD for a generic medicinal product. The facts on the RLD's label,

packaging insert, patent, literature, and clinical studies aid in developing a QTTP strategy. [Weinberg et al.,2010][Arunprasad et al.,2015] The definition of the quality target product profile (QTTP) and critical quality attributes (CQAs) of medicinal products, the completion of risk assessment (Q9, 2005) to identify CMAs and CPPs, the definition of a design space through the design of experiments (DoEs), the initiation of a control strategy, and continuous innovation and improvement throughout the product shelf life are all necessary for QbD implementation. [Ana et. al.,2018] [Pramod et al., 2016].

●Steps involved in QbD:

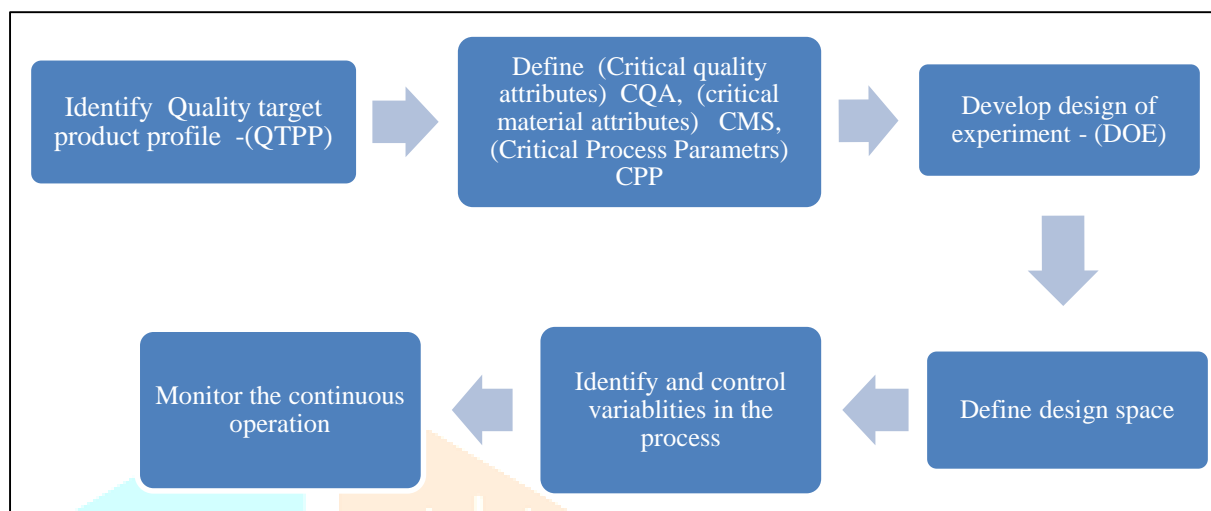


Fig no.01: Steps involved in QbD

A. Benefits of QbD [Vrushali et.al., 2016]:

- 1) It offers a higher level of assurance of the quality of drug products.
- 2) It gives the pharmaceutical business cost savings and efficiency.
- 3) It improves the sponsor's transparency and clarifies the control approach for the drug product's application and eventual commercialization.
- 4) It simplifies the process of scaling up, validating, and commercializing clear-cut, logical, and predictable.
- 5) It promotes medical innovation for unmet needs.
- 6) It lowers manufacturing costs and product rejects while improving the effectiveness of pharmaceutical production methods.
- 7) It reduces or completely avoids the possibility of costly fines, drug recalls, and compliance-related measures.
- 8) It provides chances for ongoing development.
- 9) It improves the efficiency of regulatory oversight
- 10) It facilitates regulatory and manufacturing adjustments after approval.
- 11) Post-approval CGMP inspections were more narrowly focused.
- 12) It increases the likelihood of first-cycle approval.
- 13) It minimizes the CMC supplement and supports ongoing improvement.

IV. QUALITY-BY-TESTING

Products added to the formulation throughout production process are assessed for quality under the quality-by-testing (QbT) method. If the raw materials satisfy the manufacturer's proposed, FDA-approved and USP requirements, it may be incorporated in the production process. [Arunprasad et al., 2015] The Quality by Design (QbD) strategy allows for functional versatility provided that the good parameters and the procedure parameters remain within the authorized design space. This contrast with the conventional Quality by Testing (QbT) approach, which predicts frequent batch failures with no known cause. [Nicole et. Al., 2019][Kayrak-Talay et al., 2013; Patil et al., 2015; Patil et al., 2016]

V. QUALITY TARGET PRODUCT PROFILE (QTPP)

QTPP helps in framing the root plan as the manufacturing of the product. The factors considered for QTPP for the proposed marketed product include:

1. The anticipated usage in clinical setting,
2. The administration route, the dose type, and the delivery system(s) are just a few examples.
3. The dosing strength (or doses)
4. The package's container closure system.
5. Therapeutic moiety release from the dosage form or delivery of the active pharmaceutical ingredient
6. Attributes affecting pharmacokinetic parameters for the proposed dosage form (e.g., dissolution profile and aerodynamic properties)
7. Standards for the quality of drug products, such as stability, sterility, purity, and drug release [Van et al.2014, Rathore et al.,2009].

Performance-focused CQAs should be chosen to build a QTPP for dermatological goods since this can prove that the major QbD problems for dermatological semisolid solutions. [Nicole et. al., 2019; Manish et. al., 2020]. As a result, CQAs are the features of market items that can be modified by altering the parameters used in the formulation or manufacturing processes. Examples of QTPP for topical cream [Sarika et. al., 2020]

VI. QUALITY TOOLS:

The execution of potent QbD approaches, such as process analytical technology (PAT), risk assessment, and design of experimentation (DoE), is crucial for understanding the elements of QbD in the industrial paradigm. [Arunprasad et al., 2015][Neelam et.al. 2022]

A. The un-official term “Prior Knowledge”:

Prior knowledge is regarded as an essential quality in QbD and is frequently mentioned in most seminars, presentations, workshops, conversations, and other publications associated with QbD for embracing the notion. It is imperative to have a prior knowledge for identification of the correct CQAs. Prior knowledge helps in assortment and detection of CQAs. The “prior knowledge” refers to the knowledge gained from experiences, perspectives or skills during earlier studies, but may not available in public domain. It might be proprietary in nature. [Van et al.2014]

B. Risk management:

In a risk management context, data organization for risk decision-making is called risk evaluation. It involves identifying risks as well as evaluating and choosing exposure risks. Risk recognition, analysis and evaluation of risks are the three parts of risk management, which include taking action to decrease or eliminate the risk. In order to make sure that the fundamental tools and awareness are taken into account the risk management findings should be examined during the last stage. According to ICH Q9 quality risk management, risk assessment is the process of determining the likelihood that harm will occur and how serious that harm will be.

According to ICH Q9 quality risk management, there is always some risk involved in the creation and use of pharmaceutical products. Investigations of risk are frequently influenced by a lack of knowledge or uncertainty. In-process, raw material, and final testing control strategies can be established using the study's findings to identify the essential and non-critical variables. ICH Q9 provides a representative list of primary methods and tools for quality risk management and their potential areas of use. Mentioned in them are:

- Fundamental Risk Management Facilitation Techniques (Flowcharts, Process Mapping, etc.)
- Evaluation of Criticality, Failure Mode , and Effects
- Risk leveling and filtering,
- Fault Tree Analysis,
- Hazard Operability Analysis,
- Preliminary Hazard Analysis,
- Hazard Analysis, and Critical Control Points
- Failure mode and impact assessment
- Statistical instruments [Arunprasad et al., 2015][Neelam et.al.,2022][Van et al.2014]

C. Design of experiment (DoE):

DoE is well designed and arranged strategy for figuring out how factors influencing a process relate to the process's outcomes. Plackett-Burman design, factorial design, and central composite design are specified examples. Determine the association with process-related variables and DoE using a controlled, analytical method called testing plan. DOE is a calculational technique accompanied to plan and perform research to analyze the data obtained from experimental activity. It is a kind of computer modeling that uses statistical analysis to examine the impact of a model, technique, or unit of material that controlled input parameter on the predicted response variable. Finding suitable locations, CPPs, CMAs, and design space could be made easier with its help. DoE has been proven to be beneficial in treating various pharmacological treatments and operational settings may be applied more frequently in the coming future to guarantee excellent research performance and enhanced outcomes. [Arunprasad et al., 2015][Neelam et al.2022]

D. Design space:

Design space, which has been demonstrated to assure quality, is defined by the most recent iteration of ICH Q8 as a multivariate arrangement or interrelationship of the procedure factors and input variables. The design space, perhaps for a single unit, a group of units, or the complete operation offers regulatory freedom. Working within the design area is not regarded as a shift, and it verifies a thorough comprehension of the process. The expenditures associated with time and money are yet the design space's restrictions. Additionally, if any crucial parameter is omitted from the design space construction, a negative outcome appears probably. Movement outside the FDA-approved design space is seen as a change, although changes to manufacturing within the space are not. Such adjustments call for a regulatory post-approval change process. [Arunprasad et al., 2015]

E. Response surface designs:

Surface optimization is eventually applied to the process variables discovered by the screening designs. The best processing conditions can be found using response surface designs including Box-Behnken, central composite, and three-level factorial designs. Because they are resistant to missing data and allow for the inclusion of corner and center point trials from prior factorial experiments central composite designs are recommended. On the other hand, the experiment's implementation is made simpler by using the Box-Behnken design because there are three levels for each of the factors. The drawback of this design is that a large number of center points are needed for uniform precision, and if a single datum point is missed, the result would be inconclusive. [Arunprasad et al., 2015]

F. Process analytical technology:

To make sure the process remains within its performance level, PAT is a tool used for constant offline or online process assessment of the changeable operating parameters. This is a useful tool for identifying processing errors and operational variables that can be adjusted or regulated to guarantee the product's quality. The application of PAT to assure cycle constancy in established design space is acknowledged by ICHQ8 [Neelam et.al. 2022].

When all significant sources of variation are identified, stated, and handled by the system, also when product equity performance can be calculated accurately and successfully, a system is regarded as developed from a PAT perspective. It is common to practice putting together literary works using a three-step strategy for optimizing medicinal products and manufacturing procedures, which involve observation, research, and design.

During monitoring stage, a performance measurement program enables direct or indirect systematic techniques and appropriate analysis processes to monitor all CPPs and CQAs in real-time while looking into the identified quality attribute, necessary product attributes, and processing methods. Experiments are conducted throughout the design phase to identify the critical parameters that relate to a material's function, and process parameters and input material characteristics may have a significant impact on end product quality. The CQA, CPP, and QTPP requirements for developing a PAT-based process control system are being identified using this data [Arunprasad et al., 2015, Neelam et.al. 2022].

• FEATURES OF QbD:

1) QbD is helpful for business and science:

- Batch failures are eliminated;
- Deviations are reduced;
- Regulatory compliance issues are avoided.
- Better decision-making about employee growth and technical staff empowerment are two benefits of organizational learning.

2) Advantages of QbD implementation for FDA:

The following benefits of improving the scientific basis for review are provided:

- Better coordination between review, compliance, and inspection;
- Better information in regulatory submissions;
- Improved review quality (by developing a QMS for CMC);
- Greater decision-making flexibility.
- Ensures that judgments are based on science, not empirical data;
- Involves different disciplines in the decision-making process;
- Utilises resources to deal with greater dangers

3) Profits for Industry

- Ensures improved product design and fewer manufacturing issues
- Enables the adoption of new technology to improve manufacturing without coming under regulatory inspection.
- Reduces the amount of post-market manufacturing supplements required by relying on process and risk awareness and minimizing risks. Ensures less difficulty during review
- Lowers the likelihood of a reduction in production costs overall
- Reduces waste
- Speeds up approvals
- By dealing with FDA on a scientific level rather than a procedural one, it:
- Improves interactions with FDA
- Enables continual changes to products and production processes. [Rajesh et al.,2020]

VII. CHALLENGES:

PAT and QbD demand data collection, action on that data, and capitalization of indicators and parameters, but implementation is frequently challenging when an entity does not own the necessary equipment. [Jaiprakash et al.2017]

- 1) Internal resistance within the organization.
- 2) Insufficient faith in a business case. It is presumable that the implementation of QbD for drug substance synthesis would necessitate more clinical trials or longer filing times for generic pharmaceuticals.
- 3) Lack of available technology.
- 4) Cooperation with outside parties. Complex supply chain including both suppliers and contract manufacturers are challenging to manage.
- 5) The FDA treats QbD inconsistently. It is concept that the FDA might not consistently review filings.
- 6) There are no precise industry recommendations. Companies asked the FDA for clarification on topics approved processes, standards for determining if controls are adequate, criteria for replacing testing techniques, and criteria for selecting crucial quality features.
- 7) Regulators are not prepared to handle applications for QbD.
- 8) The regulatory benefits that are presented do not encourage QbD.
- 9) Misalignment of global regulatory organizations.
- 10) The cause and main barrier to the application of QbD is a lack of knowledge about the pharmaceutical process. The end result has typically been of greater importance to pharmaceutical firms than the scientific apprehension of the process involved.
- 11) Field inspectors and the FDA review and compliance sectors must work together to find a solution to the QbD management problem.

- 12) The majority of pharmaceutical companies consider more explicit instructions on how to adopt QbD are required. Companies sought clarification from FDA on QbD terminology, approved procedures, standards by which to appraise the sufficiency of controls, criteria for testing method replacement, and criteria to select and deselect important quality attributes.
- 13) More cooperation across various business disciplines, such as innovation in processes, production, and quality control, is required for the effective deployment of QbD.
- 14) Pharmaceutical companies believe that QbD will slow down the time it takes to submit an application for approval or may give the regulatory authority further information that could pose a barrier to approval. [Jaiprakash et al.2017] [Shashank 2014]

VIII. FUTURE ASPECTS:

As seen by implementing one or even multiple QbD components into production, many companies today are beginning to consider the QbD principle and design structures to support it, signaling a positive shift towards QbD as the future development paradigm. [Singh et al., 2011]. The regulatory requirements are the main factor in QbD acceptance. The pharmaceutical corporation needs regulatory enforcement to have the products distributed-approved. Nevertheless, the QbD solution uses approaches that are economical to deliver a high-quality service. QbD eliminates the frequently applied frizzed technique of system development by providing a design space model. [Neelam et.al. 2022]

IX. CONCLUSION:

With the execution of QbD the pharmaceutical manufacturer can have better confidence for their finished products in terms of its quality, efficiency, method and process of development thereby minimizing losses. It can be concluded that the QbD approach focus on reducing product inconsistency and faults and improves product and process development, thus making it more efficient with better product quality. It also helps in post-approval management. The global regulatory bodies emphasized the significance of QbD implementation and the enormous associated benefits.

The concept of quality by design (QbD) has the potential to advance product development, production, and design. The formulations based on microparticles and nanotechnology demand detailed investigation and a lengthy procedure. Therefore, using QbD technologies to create formulations based on nanotechnology and microparticles can successfully wrap up the research processes. As time eventually, For the effective development of nano- and micro-formulations for the execution of DoE to improve the approach to design and risk prevention strategy, QbD will be recognized as a key model.

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