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QUALITY BY DESIGN (QBD) HAS BECOME A NEW CONCEPT FOR DEVELOPMENT OF QUALITY PHARMACEUTICAL PRODUCTS

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ABSTRACT

The quality by design (QbD) has become a new concept for development of Quality of a new pharmaceutical product, it is an essential part of the modern Approach to pharmaceutical quality, quality by design to ensure quality of Pharmaceuticals. In this review, the quality by design is describe and some of its Elements identified. Process parameter and quality attributes are identified for Each units operation. Benefits, opportunities and step involved in quality by Design of pharmaceutical product are described. It is based on the ICH guideline Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for Pharmaceutical quality system. It also given give application of quality by design in pharmaceutical Development and manufacturing of pharmaceutical. The aim of the Pharmaceutical development is to design a quality product and its Manufacturing process to consistently delivery the intended performance of the Product. Quality cannot be tested into product but quality should be built in by Design. It include the quality target product profile, critical quality attributes and Key aspect of quality by design. It also given comparison between product quality Quality by end product testing and product quality by design.

KEYWORDS: Quality by design(QbD), Target profiling, Critical Quality Attributes, Critical material attribute, Critical proces, Design space.

INTRODUCTION –Quality

The quality is the degree to which an object or entity satisfies a specific set of Attributes a specified set of attributes or requirement.

Quality by design

Quality by design is an approach that aims to ensure the quality of medicines By employing statistical, analytical and risk management methodology in the Design, development and manufacturing of medicine. Hence in 2002 the QBD was adopted by FDA'S regulatory framework for the 21st century "Quality systems approach to pharmaceutical CGMP and the ICH Q10 guideline system" and then by pharmaceutical.[1] The pharmaceutical Industries conscious of medicinal product quality, safety, and efficacy.[2] The main objective of the QbD is the archives the quality of product, To archive positive performance testing, ensuring combination of product and Process knowledge gained during development from knowledge of the data Process desired attributes may be construction now a day QbD approach has Been successfully enforced in common formulation development USFDA. Has Released specific QbD guide for immediate and extend release drug products as Well as biotechnological product. pharmaceutical quality by testing: In this System, product quality is ensured by raw material testing, drug substance Manufacturing, a fixed drug product manufacturing process, in-process.[3]

Material testing, and end product testing. The quality of raw material including drug substance and excipients is Monitored by testing. If they meet the manufacture's proposed and FDA Approved specification or other standard such as USP for drug substance or Excipients, they can by used be used for manufacturing of the products. Because of uncertainty as to whether the drug substance specification alone is Sufficient to ensure quality, the drug substance manufacturing process is also Tightlycontrolled. A change to the drug substance manufacturing process may Require the drug product manufacturing to file supplements with the FDA.[4]

OBJECTIVE OF QBD

1] The main objective of QbD is to achieve the quality products.

2] To achieve positive performance testing.

3] Ensures combination of product and process knowledge gained duringDevelopment.

4] From knowledge of data process attributes may be constructed.[5]

Benefits OF Qbd

1] Better understanding of the process.

2] Eliminate batch failure.

3] More efficient and effective control of change.

4] Avoid regulatory compliance problem.

5] Empowerment of technical staff.

6] Increase manufacturing efficiency, reduce cost and project rejection and Waste.[6]

Content

1] Ensure better design of product with less problem.

2] Build scientific knowledge base for all product.

3] Better interact with industry on science issues.

4] Ensure consistent information.

5] Incorporate risk management.

6] Reduce end-product testing.[7]

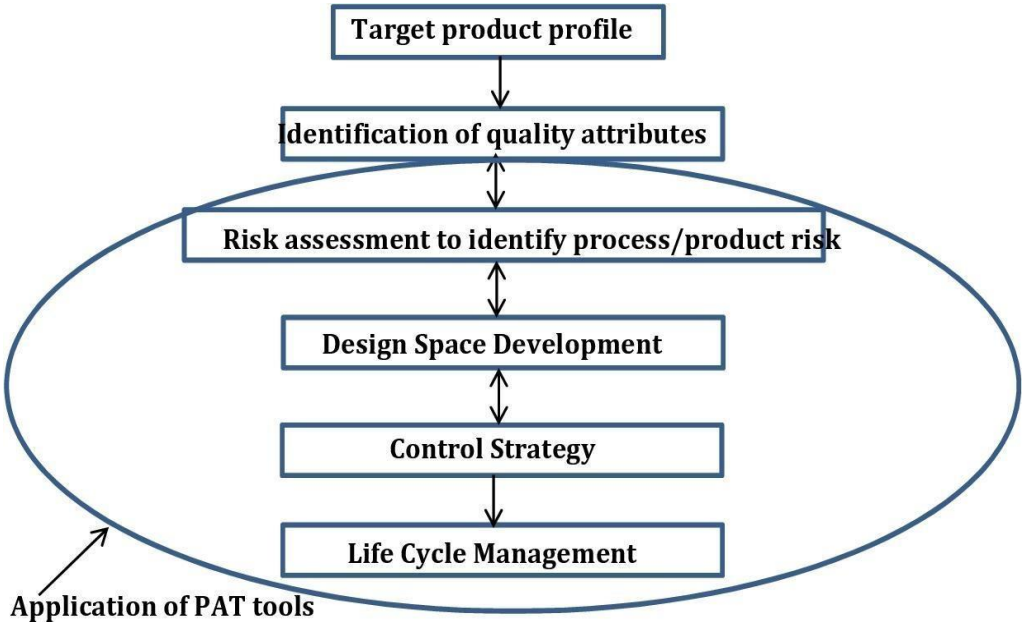


Figure 1: Elements of quality by design.

What is target profiling?

Target profiling is the process of understanding the relationship between a product and its target customers. Understanding a target profile entails analyzing where, when and why a customer buys your product. Your target profile encompasses the target audience, helping you encapsulate who responds positively to your products, services and advertisements. It

describes their most notable characteristics, such as their age, gender, location and interests. With a well-developed customer profile, a marketing team can more effectively understand its target audience, creating more personalized advertisements for both groups of customers and individual profiles.

Quality Target Product Profile (QTPP)

Quality by design" (QbD) approach has been used for developing pharmaceutical formulations. This is particularly important for complex dosage forms such as topical semisolid products. The first step for developing a product using this efficient approach is defining the quality target product profile (QTPP), a list of quality attributes (QAs) that are required to be present in the final product. These quality attributes are affected by the ingredients used as well as manufacturing procedure parameters. Hence, critical material attributes (CMAs) and critical process parameters (CPPs) need to be specified. Possible failure modes of a topical semisolid product can be determined based on the physiochemical properties of ingredients and manufacturing procedures. In this review, we have defined and specified QTPP, QAs, CMAs and CPPs that are required for developing a topical semisolid product based on the QbD approach.

Critical quality attributes

Critical Quality Attributes are the measurable characteristics that determine the identity, potency, safety, purity, and quality of a drug substance or drug product. They are the quantifiable parameters crucial for ensuring the consistency and reproducibility of the drug throughout its lifecycle.

Critical material attribute (CMA)

A process parameters (CPP) are defined as "A material or process whose variability has an impact a critical quality attribute and therefore it should be monitored or controlled to ensure desired drug product quality".

Critical process parameters

Critical process parameters in pharmaceutical manufacturing are key variables affecting the production process. CPPs are attributes that are monitored to detect deviations in standardized production operations and product output quality or changes in critical quality attributes. Examples of CPPs include temperature, pH, cooling rate, rotation speed, etc.

Design space

The Design Space is a key concept in Quality by Design, which is deduced from a Response-Surface model identified from experimental datasets. It allows manufacturers to explore combinations of multiple variables (CMAs and CPPs) usingappropriate statistical tools.

Table 1: Difference between current approach and Qbd approach.

Quality by Testing (QbT)	Quality by Design (QbD)
Current condition of assembling	
Relies on finished item testing	Desired state of manufacturing
Testing exceeds the configuration	End-product testing is for validation only
Quality achievement is never ensured	Testing balances with the design
Doesn't get much alongside government QBR	Quality is always accomplished
Time, exertion and cash devouring	Complements well with Federal QbR
Indecisiveness because of siloed conditions	Reduced expenditure of resources
Narrower operating ranges	Judicious planning using team approach
	Wider operating ranges

A pharmacological substance is categorized using the Classification System (BCS), a scientific framework, based on its water solubility, dosage, and intestinal permeability. Establishing the Control Strategy Control approach is described described as "a planned set of controls, derived from current Product and process understanding that assures Process performance and Product quality." In the QbD paradigm, the risk assessment that takes into account the criticality of the CQA and process capability establishes the control strategy. Procedural controls, in-process controls, lot release testing, process monitoring, characterisation testing, comparability testing, and stability testing are all possible components of the control plan. It's important to remember that the use of creating the control strategy Is unique to the QbD approach.

Quality Target Product Profile that Identifies the Critical QualityAttributes of the Drug Product

Taking into account the safety and efficacy of the drug product, the QTPP is a prospective description of the quality attributes of a drug product that should be attained to ensure the intended quality.[8]

- Intended use in a clinical setting, route of administration, dosage form, and delivery system(s)
- Dosage strength(s)
- Container closure system

- Therapeutic moiety release or delivery and attributes Affecting pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) appropriate to The drug product dosage form being developed
- Drug product quality criteria (e.g., sterility, purity,Stability, and drug release) appropriate for the *Intended* marketed product.

The next stage in the development of a drug product is to identify its CQAs. A CQA is a property that can be physical, chemical, biological, or microbiological. Or feature of an output material, such as a finished medication product, that must fall within a certain range, limit, or distribution in order to maintain the intended level of product quality.[9]

It should go without saying that a new product needs to be properly defined before an y development work starts.

The importance of establishing the therapeutic product's target qualities in advance ha s, however, been underestimated over time.

Therefore, there has been a loss of time and important resources as a result of the lack of a well defined QTPP. a current article by Raw.[10]

Product Design and Understanding

- A quality target product profile (QTPP) that identifies the critical quality attributes(CQAs) of the drug product.
- Product design and understanding including the identification of critical materialattributes (CMAs)
- Process design and understanding including the identification of critical process parameters (CPPs) and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs
- A control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process Process capability and continual improvement. (Google).

Over the years, QbD's focus has been on the process Design, understanding, and control, as discussed in the ICH Q8 (R2) guidance.[11]

The equal importance of product design, comprehension, and control should be highlighted. If a product can do something depends on its design. Satisfy patients' demands,

asdemonstrated by clinical research. Stability studies, which are used to corroborate this, show that product design also affects whether a product can retain its performance over the course of its shelf life. Some historical stability failures could have been avoided with this kind of product knowledge.

To create a solid product that can supply the necessary 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. Key

The following are components of product design and understanding

- Physical, chemical, and biological characterization of The drug substance(s).
- Identification and selection of excipient type and Grade, and knowledge of intrinsic excipient variability.
- Interactions of drug and excipients.
- Optimization of formulation and identification of CMAs of both excipients and drug substance.

A product development scientist must carefully analyze the physical, chemical, and biological factors in order to design and manufacture a strong therapeutic product thathas the expected CQAs.

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

Excipients can: (1) assist with dose processing Assist in product identification; (2)safeguard, support, or improve stability, bioavailability, or patient acceptance; (3) protect against, support, or improve any other aspect of the drug's overall safety, efficacy, or delivery during storage or usage.

Modes: 2To design and develop a robust drug product that has the Intended CQAs, a product development scientist must give Serious consideration to the physical, chemical, and biological Properties of the drug substance. Physical properties include Physical description (particle size distribution and particle Morphology), polymorphism and form transformation, aqueous Solubility as a function of pH,intrinsic dissolution rate, Hygroscopicity, and melting point(s). Pharmaceutical solid Polymorphism, for example, has received much attention Recently since it can impactsolubility, dissolution, stability, and Manufacturability. Chemical

properties include pKa, chemical Stability in solid state and in solution, as well as photolytic and Oxidative stability. Biological properties include partition coef Ficient, membrane permeability, and bioavailability. A product development scientist must carefully analyze the physical, chemical, and biological factors in order to design and manufacture a strong therapeutic product that has the expected CQAs. Features of the drug's active ingredient. Physical characteristics include hygroscopicity, melting point(s), polymorphism and form transformation, intrinsic dissolving rate, aqueous solubility as a function of pH, and physical description (particle size distribution and particle shape). For instance, pharmaceutical solid polymorphism has drawn a lot of attention recently due to its potential to affect solubility, dissolution, stability, and manufactureability. PKa, chemical stability in the solid state and in solution, as well as photolytic and oxidative stability, are examples of chemical characteristics. Partition efficiency, membrane permeability, and bioavailability are examples of biological characteristics.

Pharmaceutical excipients are components of a drug Product other than the active pharmaceutical ingredient. Excipients can (1) aid in the processing of the dosage Formduring its manufacture; (2) protect, support, orEnhance stability, bioavailability, or patient acceptability; (3) assist in product identification; or (4) enhance any Other attribute of the overall safety, effectiveness, or Delivery of the drug during storage or use.[12]

They Are classified by the functions they perform in a pharmaceutical dosage form. Among 42 functional excipient Categories listed in USP/NF[13] commonly used excipients include binders, disintegrants, fillers (diluents), lubricants, glidants (flow enhancers), compression aids, colors, Sweeteners, preservatives, suspending/dispersing agents, pH modifiers/buffers, tonicity agents, film formers/coatings, flavors, and printing inks. The FDA's inactive ingredients deatabase.[14]

It is well recognized that excipients can be a major source of variability. Despite the fact that excipients can alter the stability, manufacturability, and bioavailability of drug products, the general principles of excipient selection are not well-defined, and excipients are often selected ad hoc without systematic drug excipient compatibility testing. To avoid costly material wastage and time delays, ICH Q8 (R2) recommends drug-excipient compatibility studies to facilitate the early prediction of compatibility.[13]

Systematic research on drug-excipient compatibility has the following benefits: decreasing

unanticipated stability failures, which typically result in longer developme nt times and higher costs, and increasing a formulation's stability and, by extension, th e product's shelf lifeimproving knowledge of drugexcipient interactions to aid in root cause investigation in the event that stability issues arise with the drug product.

Formulation optimization studies provide important information on the following

- Robustness of the formulation including establishing Functional relationships between CQAs and CMAs
- Identification of CMAs of drug substance, excipients, And in-process materials
- Development of control strategies for drug substance And excipients

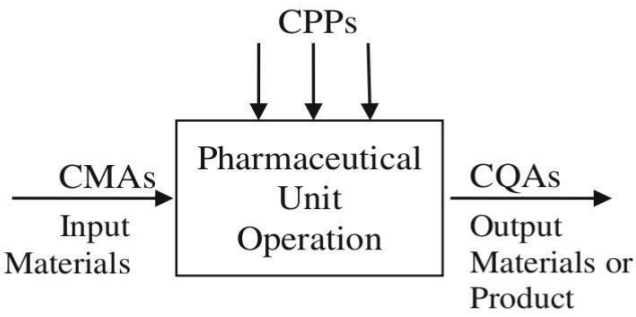
The quantity of optimization studies performed in a QbD method is not as important as the relevancy of the studies and the usefulness of the knowledge acquired for building a quality solution. Drugs are the most important thing. Therefore, the QbD isnot the same as design of experiments (DoE), but the 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 required quality of that drug component, excipient, or in- process material, a CMA is a physical, chemical, biological, or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution. CMAs are distinguishedfrom CQAs for the purposes of this essay since CQAs are for output materials. CMAsare for input materials such as drug substance and excipients, whereas intermediates and finished drug products are covered by CMAs. A CMA of an intermediate may develop from its CQA.

Intermediary for a manufacturing step farther downstream. It is unrealistic to expect a formulation scientist to look into every identified material attribute during the formulation optimization studies because there are numerous characteristics of the drug substance and excipients that may potentially affect the CQAs of the intermediates and finished drug product. Therefore, a risk assessment would be helpful in determining which material properties should be the subject of more research. The evaluation ought to draw on both the formulator’s experience and general scientific understanding. When a reasonable modification in that material attribute could have a significant impact, that attribute is crucial.

Process Design and Understanding

The design space may vary on scale and equipment. As a result, it might be necessary to justify the utilization of the desig space established at the laboratory scale at the commercial

scale. Dimensionless numbers, heat and mass transport, kinematics, geometrical considerations, and continuous verification throughout commercial manufacturing are some methods for justification. Scale-up is generally relied on general rules of thumb and trial-and-error methods because the mechanistic understanding of pharmaceutical unit functions may be limited; however, when the mechanistic understanding is dependable.



$$CQAs = f\,(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

Fig. 2: Link input critical material attributes (CMAs) and critical process parameters (CPPs) to output critical quality attributes.

Empirical models (i.e., extensive process understanding) exists, then the design space can be translated across scale.

The production of pharmaceutical items usually consists of several unit processes. For instance, the preparation of tablets via direct compression may only require mixing. compression, too.

However, unit activities may include blending, granulation, wet milling, drying, dry milling, blending for lubrication, compression, coating, and packing when tablets are m ade using wet granulation.

In these situations, the initial unit operation's output serves as the input for subsequent unit operations.

To identify CMAs, CPPs, and CQAs, process understanding could be applied to each unit operation or a group of unit operations. Figure 2 Shows an example how the CMAs and CPPs were determined, using an example of an immediate release dosageForm.[16]

Control Strategy

The knowledge gained through appropriately designed Development studiesculminates in the establishment of a Control strategy.

The CQAs of the output materials are continuously monitored at Level 1 using automatic engineering control. The most adaptable level of control is this one. Materials input characteristics To ensure that CQAs continually adhere to the defined acceptance criteria, process variables are monitored and automatically changed. In comparison to conventional end-product testing, Level 1 control offers a higher levelof quality assurance and can enable real-time release testing. It should be highlighted that implementing real-time analytics does not just require the use of process analytical technology (PAT). release testing (e.g., the use of predictive modelsas a surrogate for traditional release test, where the model may be defined in terms of traditional in-process measurements).

Level 2 consists of pharmaceutical control with reduced End-product testing and flexible material attributes and process Parameters within the established design space. QbD fosters Product and process understanding and facilitates identification Of the sources of variability that impact product quality. Understanding the impact that variability has on in-process Materials, downstream processing, and drug product quality Provides an opportunity to shift controls upstream and to reduce The reliance on end-product testing.[17]

The standard level of control employed in the pharmaceutical sector is Level 3. The comprehensive end-product testing and strictly regulated material qualities used in this control strategy Parameters for the process. Any significant change in these necessitates regulatory control due to the incomplete categorization of the causes of variability and the lack of knowledge regarding the effect that CMAs and CPPs have on the CQAs for medicinal products. Deliberations over topics like acceptable variability, the need for further controls, and the establishment of acceptance criteria consume a lot of industry and regulatory resources.

In reality, a hybrid approach combining levels 1 and 2 Can be used. ICH Q8 (R2)[18] defines a control strategy as a Planned set of controls, derived from current product and Process understanding that ensures process performance and Product quality. The controls can include parameters and Attributes related to drug substance and drug product Materials and components, facility and equipment operating Conditions, in- process controls, finished

product specifications, and the associated methods andfrequency of monitoring and control. A control strategy can include, but is not Limited to, the following.[19]

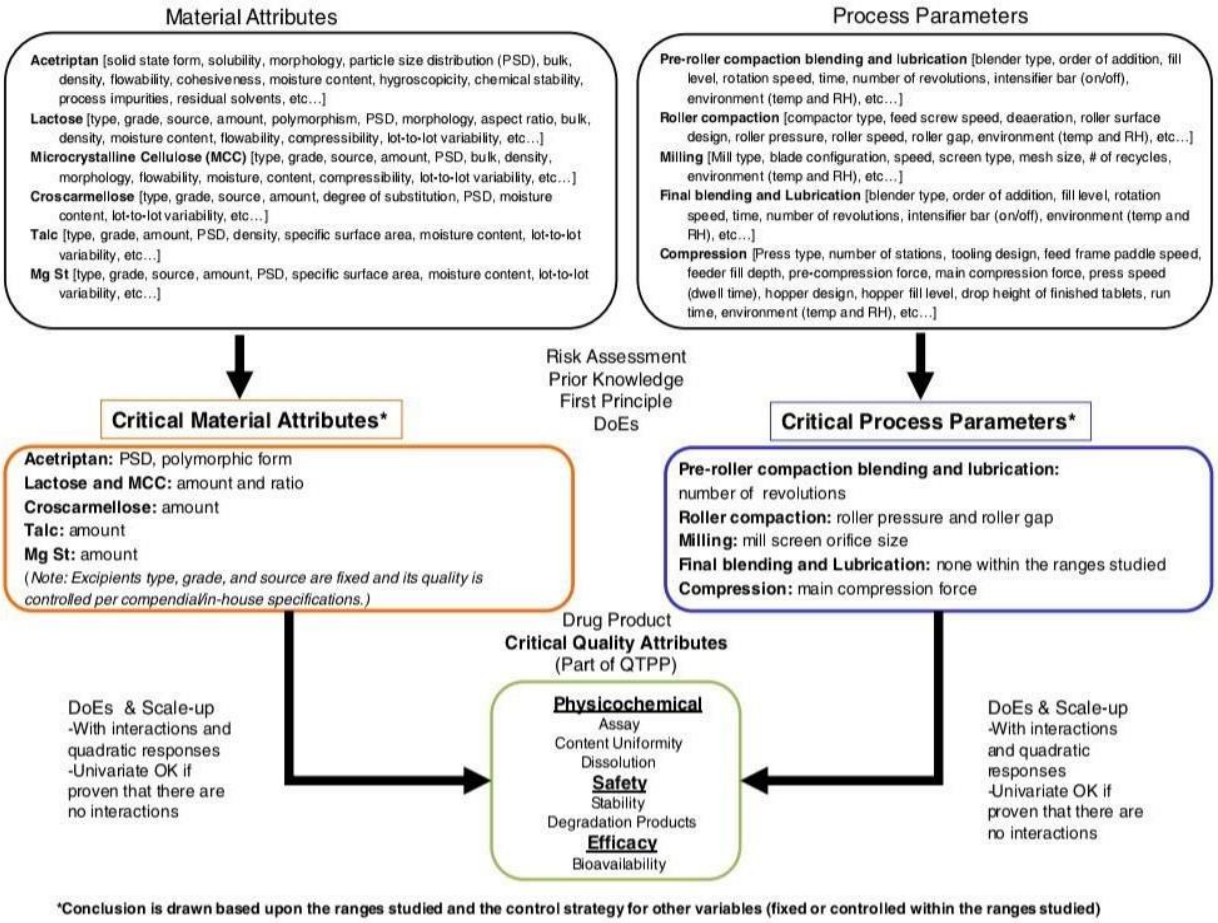


Fig. 3: Product and process understanding: an example of immediate release dosage forms.

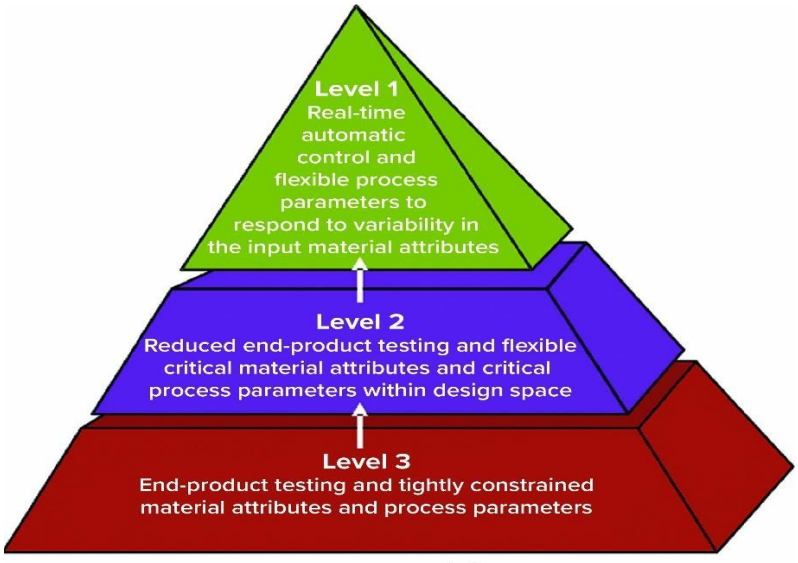


Fig. 4: Control Strategy Implementation Options.

- Control of input material characteristics (such as the drug substance, the excipient, the in-process material, and the principal packaging material) based on knowledge of their effects on Either product quality.
- In-process or real-time release testing rather than testing the final product (such as monitoring and controlling CQAs during processing);
- Controls for unit operations that affect downstream processing or product quality (such as the effect of drying on degradation and the distribution of granulate particle sizes on dissolving).

Process Capability and Continual Improvement

Process capability measures the inherent variability of a Stable process that is in a state of statistical control in Relation to the established acceptance criteria. Table III Shows the definition, calculation formula, and description of Process capability indices.[20] That are helpful for keeping tabs on how pharmaceutical production procedures are performing. Process capacity (Cp and Cpk) indices are calculated based on the inherent variability resulting from a common cause of a stable process(i.e., in a condition of statistical control).

The computation must be made when the procedure has not been shown to be in a condition of statistical control. based on sample standard deviation of all individual(observed) samples taken over a longer period of time; the Result is a process performance index (Pp and Ppk). A state Of statistical control is achieved when the process exhibits No detectable patterns or trends, such that the variation Seen in the data is believed to be random and inherent to The process.[21]

Continuous improvement is a set of activities that the Applicant carries out in order to enhance its ability to meet Requirements. Continual improvements typically have five Phases as follows.[22]

- Measure the process's major components, then gather the necessary information.
- Investigate and confirm cause-and-effect links by analyzing the data. Establish the links and make an effort to make sure all relevant elements have been taken into account. Find the defect's root cause, if there is one.
- Utilizing strategies like experiment design, you can enhance or optimize the existing process based on data analysis to produce a new, future state process. To determinethe capability of the process, set up pilot runs.
- Control the process for the future state to make sure that any target deviations are fixed

before they lead to faults. Implement control methods like Visual workspaces, production boards, statistical process control, and ongoing process observation.

PHARMACEUTICAL QUALITY BY DESIGN TOOLS

Prior Knowledge

The phrase "prior knowledge" has been widely used in workshops, seminars, and presentations even though it is not formally defined. Applicants frequently try to claim past knowledge as a "legitimate" justification in regulatory submissions. A justification for using other justifications than scientific ones or for undertaking the required scientific investigations.

A familiarity with someone or something can be referred to as knowledge, which can also include information, facts, descriptions, and/or abilities gained through training or education. The prefix "prior" in "prior knowledge" refers to not only Meaning "previous," but it also connotes ownership and privacy; it is not open to the public. As a result, prior knowledge cannot be acquired for the purposes of this paper through education but only by experience. Public knowledge can be defined as knowledge acquired through schooling or public literature. In the QbD paradigm, "prior knowledge" often refers to information gleaned from prior experience but not from publicly accessible literature. The exclusive knowledge, comprehension, or competence that applicants have acquired via prior studies is referred to as prior knowledge.

Risk Assessment

The manufacturing and use of a drug product, including its components, "necessarily entail some degree of risk," according to ICH Q9 quality risk management. The level of effort, formality, and documentation of the quality risk management process should be proportionate with the level of risk, and the appraisal of the risk to quality should be founded on scientific knowledge and eventually lead to the protection of the patient.[4]" The aim of ICH Q9 is to provide a systematic approach to quality risk management; risk assessment in product development is not expressly addressed.

However, risk assessment in product development can also be done using the risk assessment tools mentioned in ICH Q9. The purpose of risk assessment prior to development Studies is to identify potentially high-risk formulation and Process variables that could impact the quality of the drug Product. It helps to prioritize which studies need to be conducted And is

often driven by knowledge gaps or uncertainty.

Study Results determine which variables are critical and which are not, Which facilitates the establishment of a control strategy. The Outcome of the risk assessment is to identify the variables to be Experimentally investigated. ICH Q9.[23]

CONCLUSION

The goals of pharmaceutical QbD implementation are Reduces product variability and defects, which improves Product development and production efficiency and Manage changes after approval. This is achieved through planning Robust formulation and manufacturing process and validation of clinically relevant specifications. The main elements Pharmaceutical QbD may include QTPP, product design And understanding, process design and understanding, and scope Up, control strategy and continuous improvement. In order to be effective, QbD needs to support a generic product development company whose main goal is to submit applications first. Instead of focusing on the quality of the ANDA, many R&D companies in the generics business judge success based on the quantity and timing of ANDA filings. If we include the Agency's efforts to guarantee that commercial goods maintain bioavailability claims made during development.

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