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A COMPREHENSIVE UNDERSTANDING ON VARIOUS ASPECTS OF QUALITY BY DESIGN – A REVIEW.

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Abstract
Quality by Design (QbD) approach in the pharmaceutical industry which seeks to explore the principles, methodologies, and applications of QbD, and to highlight its significance in ensuring the quality of pharmaceutical products. Today, the new approach to pharmaceutical quality is called Quality by Design. It explains how to apply "Quality by Design" to guarantee pharmaceutical quality. This review identifies some of the components of Quality by Design and describes it. For every unit operation, process parameters and quality attributes are determined. The advantages, prospects, and procedures associated with pharmaceutical product quality by design are explained. The Q8 guidelines for pharmaceutical development, Q9 guidelines for quality risk management, and Q10 guidelines for pharmaceutical quality systems form its foundation. It also discusses the use of Quality by Design in the creation and production of medications. The goal of pharmaceutical development is to create high-quality products and manufacturing processes that reliably produce the desired results. Products cannot be assessed for quality; instead, quality should be included into the design. Key components of Quality by Design, as well as the Quality goal product profile and essential quality criteria, are included. Additionally, it provides a comparison of the product quality as determined by Quality by Design and as determined by final product testing. ICH Guidelines serve as the cornerstone of Quality by Design.

KEYWORDS: RP-HPLC, Analytical quality by design (AQbD), Central Composite Design, Quality Risk Management.

1.INTRODUCTION

Pharmaceutical industry is constantly searching the ways to ensure and enhance product safety, quality and efficacy.[1] However, drug recalls, manufacturing failure cost, scale up issues and regulatory burden in recent past produce huge challenge for industry. In traditional, the product quality and performance are predominantly ensured by end product testing, with limited understanding of the process and critical process parameters. Regulatory bodies are therefore focusing on implementing quality by design (QbD), a science based approach that improves process understanding by reducing process variation and the enabling process-control strategies.Instead of relying on finished product testing alone, QbD provides insights upstream throughout the development process.

As a result, a quality issue can be efficiently analyze and its root cause quickly identified. QbD requires identification of all critical formulation attributes and process parameters as well as determining the extent to which any variation can impact the quality of the finished product.
In the area of pharmaceutical quality; Food and drug administration (FDA) announced proposed amendments to "Current Good Manufacturing Practices" (cGMP) in 2002,[2] with an emphasis on establishing a 21st century outlook on pharmaceutical manufacturing in order to establish a more systematic science and risk based approach to the development of pharmaceutical products. The initiation of the cGMPs for the 21st Century and the publication of the Process Analytical Technology (PAT)[3] guidance in 2004 by the FDA gave the way for the modernization of the pharmaceutical industry.
After that, ICH (International Conference on Harmonization) discussions in July 2003 (Brussels) agreed a consensus vision to develop a harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to risk management and science. All the major objectives with regard to quality issues are being addressed by the ICH guidelines. The three ICH guidelines which throw light upon quality-by-design and related aspects include
ICH Q8 Pharmaceutical development.[4]
ICH Q9 Pharmaceutical risk management[5] and
ICH Q10 Pharmaceutical Quality systems.[6]

In fact, the ICH guideline Q8 is sub-divided into two parts: part one deals with pharmaceutical development and Part II is the annex to the guideline which states the principles for Quality-by-Design. According to ICH Q8(R2) guideline, Quality by Design (QbD)[7] is "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and Process control, based on sound science and Quality Risk Management".This concept was introduced by Dr. Joseph M. Juran. He belived that quality should be designed into a product, and that most quality crises and problems relate to the way in which a product was designed. Qbd is a word that ensures quality which means End users satisfaction or To match the expectation of standards ,where design means structural planning .Hence Qbd ensures desired quality by planning .Quality should be enhanced into the process than tested into the final analytical process results.
Qbd involved in the development of new molecule in Preclinical studies[8] Clinical studies[9]

Submission of market approval and Stability studies. **In manufacturing process like P**rocess design, Design space Quality control **Control strategy** [10] Continuous development Risk based decision [11] Product performance.

1.1 Benefits of QbD: Eliminate batch failures, Minimize deviations and costly investigations, Avoid regulatory compliance problems, Empowerment of technical staff, Efficient, agile, flexible system. Increase manufacturing efficiency, reduce costs and project rejections and waste, Build scientific knowledge base for all products, Better interact with industry on science issues, Ensure consistent information, Incorporate risk management, Reduce end-product testing, Speed-up release decision.

1.2 An Overview of Qbd: Begins with a target product profile that describes the use safety and efficacy of the product .Gathering the relevant prior knowledge about the drug substance, excipients and process into a knowledge space and using the risk assessment to prioritize knowledge gaps for further investigation.Designing a formulation and identifying the cirtical material (quality) attributes of the final product that must be controlled to meet the target product quality profile.Designing a manufacturing process to produce a final product having these CMA
Identifying the CPP and input raw material attributes that must be controlled to achieve these CMA of the finial product.Establish a control strategy for the entire process that may include input material. Controls process controls and monitors,design space around individual or multiple unit operations or final product tests.

1.3 Key elements of Qbd in pharmaceutical development [12]

Define the Quality Target Product Profile.
Identify the Quality Attributes.
Perform a Risk (Assessment) Analysis.
Determine the Critical Quality Attributes and Critical Process Parameters.
Determine the Design Space.
Identify a Control Strategy.

1.4 Quality Target Product Profile (QTTP) [13]:

According to ICH Q8(R2), QTTP is "Prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product".
Basically it is a tool for setting the strategy for drug development. Recently QTTP is widely used in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management.
It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label. The QTTP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. QTPP is related to identity, assay, dosage form, purity, stability in the label.
For example, a typical QTPP of an immediate release solid oral dosage form would includes tablet Characteristics, Identity, Assay and Uniformity, Purity/Impurity, Stability and Dissolution.
It is important to acknowledge that QTPP should only include patient relevant product performance elements.For example, tablet density or hardness may be included as a specification for process monitoring but may not be included in QTPP. Also, if particle size is critical to the dissolution of a solid oral product, then the QTPP should include dissolution but not particle size.

1.5 Critical quality attributes (CQAs) [14]:

Once QTPP has been identified, the next step is to identify the relevant CQAs. A CQA is defined as "A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality".
CQAs are generally associated with raw materials (drug substance, excipients), intermediates (in-process materials), and drug product. Drug product CQAs are the properties that are important for product performance, that is, the desired quality, safety, and efficacy.
This indicates that CQAs are subsets of QTPP that has a potential to be altered by the change in formulation or process variables. For example, QTPP may include additional quality attributes of the drug product such as strength and dosage form, which are not the part of CQA as it will not change during drug development process.

However, QTTP attributes such as assay, content uniformity, dissolution, and permeation flux will also be a part of CQA as they may be altered by formulation or process variablesFor example, the CQAs of drug substance and drug product identity, strength, purity and potency.
Identification of CQAs is done through risk assessment as per the ICH guidance Q9. Prior product knowledge, such as the accumulated laboratory, nonclinical and clinical experience with a specific product-quality attribute, is the key in making these risk assessments.Such knowledge may also include relevant data from similar molecules and data from literature references. Taken together, this information provides a rationale for relating the CQA to product safety and efficacy.

1.6 Quality risk management (QRM) [15]:

The FDA defines a Risk Management as, a strategic safety program designed to decrease product risk by using one or more interventions or tools.It is systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product life cycle .

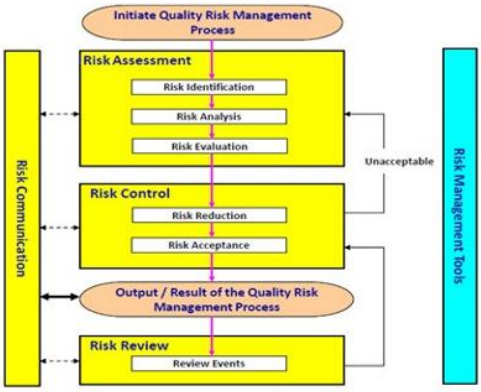


Figure.3:- Initiation of Quality risk management Process

The ICH Q9 guideline: Quality Risk Management provides a structure to initiate and follow a risk management process. The relevant tools of QRM are as follows:

1.7 Determination of Critical Process Parameters [16]

A critical process parameter (CPP) is any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency.

A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the QTPP.

Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider.

Thus the first step in classifying parameters is to define the range of interest which we call the potential operating space (POS).

The POS is the region between the maximum and minimum value of interest for each process parameter.

Criteria for identifying critical and non-critical parameters are that a parameter is non-critical when there is no trend to failure within the POS and there is no evidence of interactions within the proven acceptable range (PAR), which is the range of experimental observations that lead to acceptable quality.

1.8 Design space [17]

ICH Q8(R2) defines design space as " the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change.

Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval."Design space may be constructed for a single unit operation, multiple unit operations, or for the entire process.

Though according to FDA guideline, defining design space is optional since the product and process understanding can be established without a formal design space, nevertheless, such approach can assist to better understanding and attain overall control of a system.The Design Space is linked to criticality through the results of risk assessment, which determines the associated CQAs and CPPs.It describes the multivariate functional relationships between CQAs and the CPPs that impact them, and should include their linkage to or across unit operations.Such relationships are arrived at by iterative application of risk assessment and experimental design, modeling, as well as the use of

literature and prior experience.Methods for determining design space included: one-variable-at-a-time experiments, statistically designed experiments, and modeling approaches.
Methods for presenting design space included graphs (surface-response curves and contour plots), linear combination of parameter ranges, equations, and models. Alternatively, the design space can be explained mathematically through equations describing relationships between parameters for successful operation.

1.9 Control Strategy

ICH Q10 defines a control strategy as "a planned set of controls derived from current product and process understanding that assures 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 and frequency of monitoring and control."

A control strategy normally include input material controls, process controls and monitoring, design space around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality.The finished drug products are tested for quality by assessing if they meet specifications. In addition, manufacturers are usually expected to conduct extensive in process tests, such as blend uniformity or tablet hardness.A QbD based control strategy for blending process that Pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables to assure the quality of the finished product. The end product testing only confirms the quality of the product
.

1.9.1 key challenges are the most problematic for QbD adoption [18]:

These challenges are evaluated by their relevancy against different drug types as well as different levels of adoption.
The first four challenges occur within companies:

i. Internal misalignment (Disconnect between cross functional areas, e.g., R&D and manufacturing or quality and regulatory)
ii. Lack of belief in business case i.e. there is a lot of uncertainty over timing of and investment requirements for QbD implementation.
iii. Lack of technology to execute (e.g., Difficulty managing data, limited understanding of Critical Quality Attribute (CQA) implications)
iv. Alignment with third parties (i.e., How to implement QbD with increasing reliance on suppliers and contract manufacturers?)

The next six challenges are directly related to the regulatory authority:

I. Inconsistency of treatment of QbD across regulatory authority
II. Lack of tangible guidance for industry
III. Regulators not prepared to handle QbD applications
IV. The way promised regulatory benefits are currently being shared does not inspire confidence
V. Misalignment of international regulatory bodies
VI. Current interaction with companies is not conducive to QbD

It is accepted that the challenges and concerns associated with the implementation of QbD can only be resolved if there is efficient communication between the industry and the regulatory bodies.

1.9.2 Applications of QbD in Pharmaceutical Industry [19]:

In Pharmaceutical Industry, the applications of Quality by design implementing in Pharmaceutical Drug Discovery, pharmaceutical product development, Analytical quality by design, Clinical Studies, Pharmacovigilance and regulatory affairs.

2. QBD IN DRUG DISCOVERY AND R & D

QbD is a systematic approach to pharmaceutical development for drug discovery and R&D [20] in designing and developing formulations and manufacturing processes that can generate a prescribed product quality**.**

2.1 To calculate Molecular Properties :like Physicochemical, ADME & Toxicity.
For Physicochemical properties like Aqueous Solubility, Boiling Point, Log P.
For ADME:Blood Brain Barrier Permeation, Cytochrome P450 Inhibitors and Distribution.
To know Toxicity like Acute Toxicity, Mutagenicity

2.2 To Process, Analyze, and Manage All Analytical Data:
The Spectrus platform uniquely offers software applications for multi-technique, vendor-neutral analytical data processing, analysis, and data management.

3. QBD IN PRODUCT DEVELOPMENT AND REGULATORY EXPECTATIONS

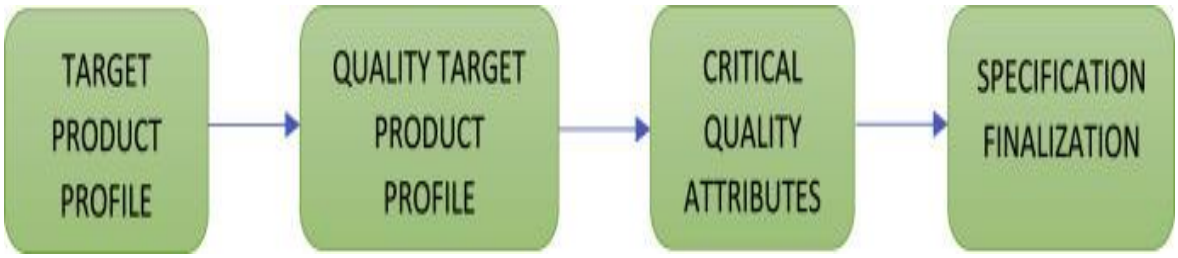
QbD in Product Development and Regulatory Expectations [21] the Quality has to be built in the product as well as services through proper planning so that forth coming failures can be avoided.

3.1 Product development by qbd [22]:

The important components of product development by QbD are target product profile (TPP), target product quality profile (TPQP), design and development of product, developing the manufacturing process, identifying the CQA, assessment and management of the risks involved in the process, establishment of design space, and defining a control strategy for a product to stay within the design space.

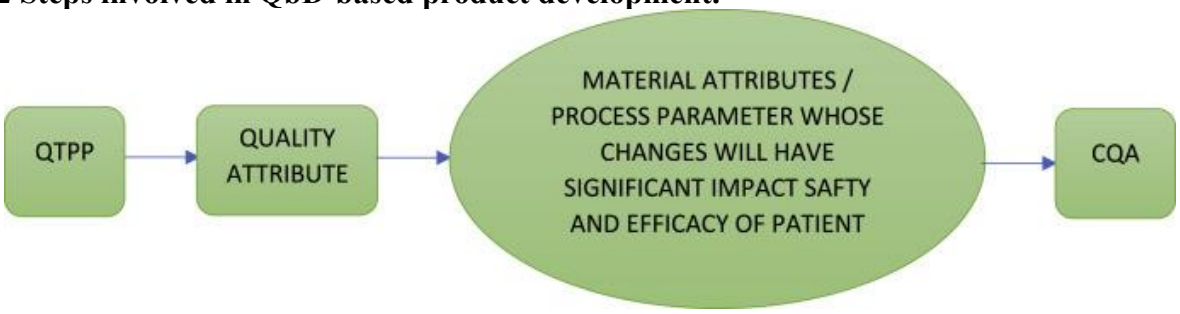
Control strategy is the knowledge driven from the relationship between formulation and manufacturing process variables that must be controlled in manufacturing a product of consistent quality. Product lifecycle management further adds to the knowledge base, helps in continuous product monitoring and improvement.

3.1.1 Order of QbD-based product development [23]:



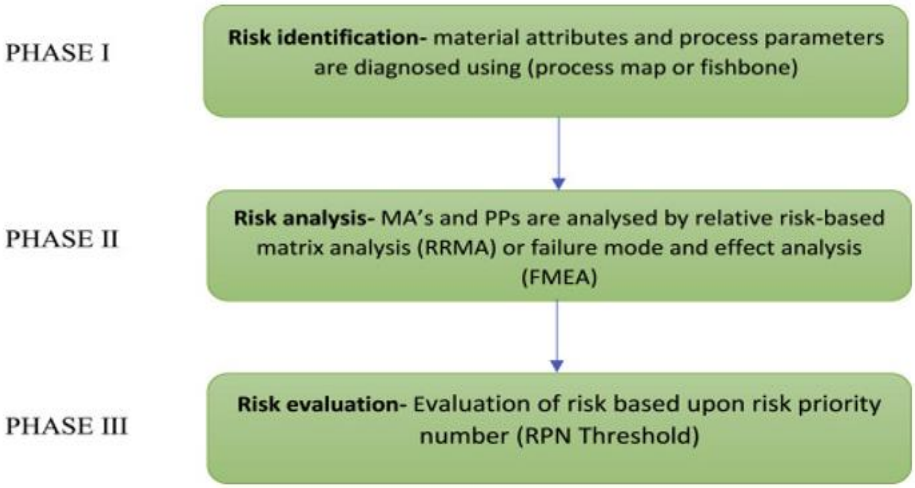
Quality cannot be tested into products; it should be built-in or should be by design" is the current approach of FDA to a manufacturing process. FDA defined PAT as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

3.1.2 Steps involved in QbD-based product development.



Phase 1: Define Phase Defining the targets or the objective of drug product development, these targets or objectives should be achieved to ensure the desired quality of the drug product required for safety and efficacy.
Phase 2: Measure phase Measuring the critical quality attributes out of quality attributes (QA's) because deviation or out of specification of CQA's will have a definite impact on safety and efficacy of customer or patient.
Phase 3: Analyse phase Identifying critical process parameters (CPPs) and critical material attributes (CMAs) and further analyzing risk factors through SIPOC, RRMA, FMEA, ANOVA.
Phase 4: Improve phase Designing the design of the experiment and developing and verifying design space. It can be done by first screening experiments and then optimizing experiments.
Phase 5: Control phase Implementation of control strategy and control critical factors with control space and continue improvement.
From DoE and design space, control space for every CMA and CPP's proposed for future commercial manufacturing batches so that no out-of-specifications.

3.1.3 Impact of critical quality attributes [24]



3.1.4 Phases of Risk Assessment.

Low risk	Broadly acceptable risk
Medium risk	The risk may be acceptable, and may or may not impact product quality.
High risk	Risk is unacceptable, and will have a significant impact on quality

3.1.5 Critical Quality Attribute (CQA's)

It is important to identify the critical quality attributes, i.e., those defining purity, potency, and surrogate for efficacy. It is based on the impact of quality attributes on the safety, efficacy & quality of the product are identified by quality risk management and experimentation to determine the variation of quality product. Potential CQAs are derived from the QTPP and guide product and process development.

CQAs are identified by quality risk management and experimentation to determine the effect of variation on product quality.

3.1.6 Risk assessment Identification of Critical material attributes and Critical process Parameters[25]

Risk assessment is an important element used in quality risk management that can aid in identifying which critical material attributes and critical process parameters potentially have a significant impact on product CQAs. Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. The evaluation of the quality risk should be based on both scientific knowledge as well as therapeutic benefit to the patient.

3.1.7 Identification of Critical Process parameters [26]

CPPs are responsible for ensuring the CQAs & it is identified from a list of potential CPPs using risk assessment. It is a measurable input material attribute or output material attribute of a process step that should be controlled to achieve the desired product quality as well as process uniformity.
Further, CPPs can be classified into 2 types.

- Critical parameter- A realistic variation in parameter can cause the product to fail to achieve CQAs and QTPP.
- Non-critical parameter- No failure in QTPP determined within the potential operating space & no interactions with other parameters in the established suitable range.

3.1.8 Qualitative risk base matrix analysis

It can be further divided into three types:
Design space
Development of process analytical technique
Implementation of control strategy

3.1.9 Design space:

Working with design space is not considered as a change. Design space can be established by implementation of design of the experiment. Multidimensional combination of & interaction of input variables (material attributes) and process parameters that have been demonstrated to provide Quality Assurance.

3.2 Development of Process Analytical Techniques [27]:

Process analytical technology (PAT) has been defined by the Food and Drug Administration (FDA) "as a method to design, analyze, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect of Critical Quality Attributes.

3.2.1 Implementation of control strategy [28]:

To ensure batch-to-batch uniformity in evaluation parameters and quality and performance of the finished drug product during the commercialization process. In order to ensure a consistent desired product quality, a control strategy should be designed and managed. A control strategy can include raw material specifications, process controls, in-process testing, and finished product testing.

3.3 Product Lifecycle Management And Continual Improvement [29] :

The Knowledge gained from technology transfer activities provide useful inputs for manufacturing process, control strategy, and process validation which forms the backbone for continued product and process improvement. The knowledge resulting from the commercial manufacturing should also be utilized for continual product improvement. Products of desired quality are obtained and the potential areas of continual improvement are identified by the throughout the life cycle of the product. The review should include regulatory aspects, customer satisfaction, process and product performance, and the corrective actions and preventive actions taken. The scope of improvement to manufacture process and product quality should be identified and considered by the management review system throughout the life cycle of the product.

Figure.8: Product life cycle Managements

3.3.1 Process analyzers [30]:

Significant advancement have been observed for the process analyzers in recent past and even nondestructive methods are now available for collecting data related to the biological, physical, and chemical attributes of the materials. It involves at-line, on-line, or in-line measurements. Process analyzers are able to provide much data. Real-time control and quality assurance during manufacturing are possible with modern process analyzers.

3.3.2 Process control tools [31]:

According to PAT, a process end point is the achievement of desired material attribute rather than a time-defined end point. Process control tools are used to ensure effective control of all product CQA. It also measures the ability and reliability of process analyzers to measure critical attributes.

3.3.3 Change management system:

A Proper change management system should be established in a company which should be able to monitor, approve, and implement changes. The evaluation of the changes is carried out by quality risk management. product quality and process performance should be evaluated properly by the management review board of the company throughout the life cycle of the product.

3.3.4 Failure Mode Effects Analysis [32]:

This tool can be used to identify any inappropriate changes occur in the development of the product. The risk involved in changing a process can also be limited using failure mode effects analysis Failure

mode, effects, and criticality analysis is most used for failures and risks associated with manufacturing processes.

3.3.5 Fault tree analysis [33]:

It is an excellent tool for evaluating multiple factors affecting product quality. It is useful for both RA and monitoring. It is mainly depending upon the understanding of the process to identify the causative factor.

3.3.6 Continuous improvement and knowledge management tools [34]:

Throughout the life cycle of a product, data can be collected, analyzed, and the knowledge can be utilized for the continual product and process improvement.

3.4 Regulatory expectations of QBD:

Quality is an important factor for all regulatory bodies for pharmaceutical products. Quality means customer satisfaction in terms of service, product, and process. Customer satisfaction can be achieved by two ways i.e. features and free from deficiencies in goods. The features like performance, trustworthiness, robustness, ease of use, and serviceability have to built in the product and such product should be free from deficiencies.

3.4.1 Regulatory aspects of QBD:

In USFDA asked participating firms to submit chemistry manufacturing control (CMC) information demonstrating application of QbD as part of New Drug Application. QbD in-volves thorough understanding of process; a goal or objectiveis defined before actual start of process Design space and realtime release risk assessment are other parameters for implementation of QbD. International conference on harmonizationin its Q8 pharmaceutical development, Q9 quality risk assessment and Q10 pharmaceutical quality system gives stringent requirements regarding quality of product. FDA also states the importance of quality of pharmaceutical products by giving process analytical technique which is a framework for innovative pharmaceutical product development manufacturing and Quality assurance.

3.5 Regulatory bodies:

- **ICH (1999 [35]) :** Defines the thought of quality and assists within the institution of worldwide specifications for brand new drug substances or drug product.
- **FDA (2004a)[36]** : Outlines the QbD thought and summarizes initiatives to encourage science-based policies and innovation in pharmaceutical development and production. Proposes risk assessment as a tool to gauge the impact of variations in method inputs on product quality.
- **FDA (2004b):** Introduces the PAT framework. Defines method understanding, vital quality attributes, and important method parameters, and identifies PAT tools.
- **FDA (2004c):** Defines the manufacturing method because of set of activities associated with product style method style and technology transfer .It defines the conception of risk for pharmaceutical quality and provide principles samples of tools for risk assessment and management.
- **ICH (2008):** Describes a model for a good quality management system[37] throughout the lifecycle of the merchandise. Outlines the management strategy and continuous improvement ideas.
- **ICH (2009):** provides an outline of qbd in product development. Defines most of the QbD Paradigms (quality TPP, important quality attributes, risk assessment, style, area, and management strategy), providing tips for his or her implementation or submission of technical documents.
- **ICH (2010):** Proposes queries and answer sessions to facilitate the implementation of the Q8/Q9/ Q10 tips. Provides many clarifications and therefore restrictive perspective in the main centred on qbd topics as style area real time unleash testing and management strategy.

- **ICH (2011)**: provides a guide for ICH Q8/Q9/Q10 /Q11 with stress on criticality identification, management strategy, style area, and method validation. Introduces the employment of modelling as a tool of implementing qbd at each style of development.

3.6 Regulatory challenges:

In a qbd idea restrictive burden is a smaller amount as a result of there are a unit wider range and limits supported product and method understanding. Changes among these ranges and limits don't need previous approval.

3.6.1 The challenges associated with regulative authority:

- Inconsistency of treatment of QbD across the administrative body.
- Regulators not ready to handle QbD applications.
- The approach to secure regulative advantages is presently being shared doesn't inspire confidence.
- Misalignment of international regulative bodies.
- Current interaction with corporation is not causative to Qbd.
- Lack of triangle steering for business.
- Internal placement (Disconnect between cross-practical areas eg. R and D and producing or quality and regulation.
- Lack of belief in the business case, that is, there are loads of uncertainty over the temporal order of and investment necessities for QbD implementation.
- Lack of technology to execute (eg. Issue managing information, restricted understanding of vital quality attribute.
- Alignment with third parties (i.e the way to implement QbD).

3.7. Current status of regulatory bodies[38]:

The ICHs pharmaceutical Development guidelines, ICH Q8, the objective is to systematically deliver a high-quality product by building correct controls, understanding of your producing method, and observance of the correct parameters and attributes. It is a scientific risk based holistic, and proactive approach to pharmaceutical development and is a deliberate style effort from product conception through development with a full understanding of however product attributes and processes relate to product performance.

4. QBD IN ANALYTICAL METHOD DEVELOPMENT:

Analytical method development [39] is an important part of the drug development process therefore the quality principles which have been described in the ICH guideline Q8 (R2) should be implemented to eliminate risks or failures.

There are several software solutions available for analytical High-Performance Liquid Chromatography (HPLC) method development using the Quality by Design (QbD) principle**.**

4.1 Benefits of Analytical QbD:-

Increased understanding and control.
Beyond traditional ICH procedure of method validation.
Flexibility in analysis of API, impurities in dosage forms, stability samples, and metabolites in biological samples
Reduction in variability in analytical attributes for improving the method robustness
To keep the values of analytical attributes within the pharmacopoeia monographs, and away from Out Of Specification (OOS) limits
Smooth process of method transfer to the production level
No requirement of re-validation within MODR QbD Principles for Analytical Method Development:

5. QBD IN PHARMACOVIGILANCE

5.1 Pharmacovigilance [40]

The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.

5.2 Adverse effects:

an adverse effect (AE) is a harmful and undesired effect resulting from a medication or intervention and procedures.

5.3 Risk Management plan

ICH Q9 quality risk management indicates that "the manufacturing and use of a drug product, including its components, necessarily entail some degree of risk.… The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient and the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk .The purpose of ICH Q9 is to offer a systematic approach to quality risk management and does not specifically address risk assessment in product development.
Applicants are responsible for ensuring the safety profile of their medicine is adequately characterised at the time of submitting their marketing authorisation application . Applicants are required to submit a risk management plan as part of their marketing authorisation application. Risk management plans describe existing knowledge on the safety of a medicine and future pharmacovigilance activities designed to further study or monitor the product's safety.

5.4 POSTMARKETING [41]

Postmarketing drug surveillance refers to the monitoring of drugs once they reach the market after clinical trials. It evaluates drugs taken by individuals under a wide range of circumstances over an extended period of time. Such surveillance is much more likely to detect previously unrecognized positive or negative effects that may be associated with a drug. The majority of postmarketing surveillance concern adverse drug reactions (ADRs) monitoring and evaluation.

6.CONCLUSION

QbD is increasingly becoming an important and widely used technique in Pharmaceutical Drug Discovery, pharmaceutical product development, Analytical quality by design, Clinical Studies, Pharmacovigilance and regulatory affairs.
While QbD is most effective when it is employed at a product/process design level, it should also be accomplished in the manufacturing and quality assurance environments.
Implementing QbD concept in product development provide quality medicines to patients, production improvements to Manufacturers with significantly reduced batch failures and drug regulatory bodies will have greater confidence in the robust quality of products.
In Traditional approach, Starts with hit and trial approach to meet method intent whereas QbD approach Starts with predefined objective.
Systematic evaluation of individual variables.
Performance qualification and verification are monitoring continuously throughout life cycle.
As such QbD is becoming a promising scientific tool in quality assurance in pharmaceutical industry.

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