IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

QUALITY BY DESIGN (QBD) IN PHARMACEUTICAL FORMULATIONS WITH SPECIAL EMPHASIS ON INJECTABLE HYDROGELS PREPARATIONS FROM DISCOVERY TO PRACTICE

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Abstract: Recently, the concept and idea of "Quality by Design" (QbD) is attracting huge attention among pharmaceutical industries for maintaining Quality or for maintaining the appropriate quality standards in the products. It serves as a link between industrialists and drug regulatory officials to approach a scientific, risk-based, holistic, progressive approach to the development of pharmaceutical products. Its priorly focuses on designing and developing injectable hydrogel preparations from such manufacturing processes to ensure the predefined quality of the preparation. of the QbD elements include defining the target product quality profile, designing product and manufacturing processes, identifying critical quality attributes, process parameters, and sources of variability & controlling manufacturing processes to produce consistent quality over time The aim and purpose of this article is to discuss the concept of pharmaceutical Quality by Design implied on injectable hydrogels preparations and to explain that how it can be proven helpful to ensure pharmaceutical quality & formulation development.

Keywords: Good manufacturing practices (GMP) Quality by Design (QbD), Target Product Quality Profile (TPQP), Critical Quality Attribute (CQA), Critical Process Parameter (CPP), and Quality Risk Management (QRM).

INTRODUCTION

As everyone knows that today's era is the era of competition and quality every day coming day new, better discoveries and improvements are being brought in every industry, due to which human life has become even easier and more convenient as far as we talk about the pharmaceutical industry, the pharmaceutical industry is also going through a changing phase and trying to adopt new techniques and new methods, as you know about the journey of the pharmaceutical industries till date had been very good and dedicated to improving the human life and lifestyle.

The pharmaceutical industry has grown twice as much day and night in the last few decades as a result of its human life has improved on a very large scale, but it is also well known that even today, despite these improvements, the pharmaceutical industry is still not producing a quality based best product completely, this is because of the reason that the pharmaceutical industries have always placed a high priority on the final product when creating pharmaceutical formulations, any mistake made in the beginning is very difficult to detect, causing entire batches numbering in the thousands to spoil. Because their testing used to happen much later, just before the final product was made, there have been many occasions when such disturbances have forced the cancellation of the entire batch. Due to this reason, it is necessary to allocate new discoveries and new better, improved techniques. In the pharmaceutical world, it has always

been a tough task to do risk management, for which many commendable steps have been taken by the pharmaceutical industry which includes many quality checks, implementation of good manufacturing practices to some extent, and installment of semi-automatic and automatic plants to avoid the human interruption during the processing. But in spite of this, the outcomes from the pharmaceutical industry still need some improvements.

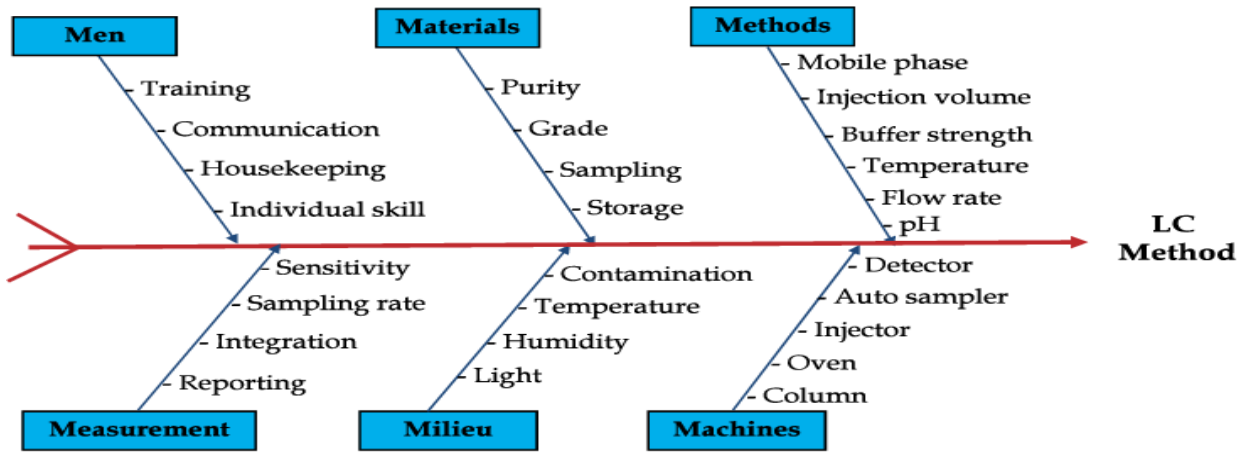

fig.1 understanding QbD overview from fishbone diagram

As far as when different products such as inhalers, infusion, implants, radio techniques,

nanotechnology, sustained release tablets, controlled release tablets, self-healing hydrogels, quick responding injections, etc. formulations had been invented and formulated by the pharma industries, but the new invention that is being brought under consideration nowadays is the injectable hydrogels. Injectable hydrogels are more efficient when compared to other oral and parental drug formulations. Quality by Design can prove to be a milestone by using its principles According to QbD, the pharmaceutical industries have to improve their entire process by making little changes throughout, so that in the end the pharmaceutical product that comes out will not get failed. If a product is made in accordance, it will also be successful in stopping the problem at its inception. After all, any manufacturing should begin by adhering to the ICH Quality by Design principles by implementing incremental adjustments throughout the entire process, such as 100% implementation of Good Manufacturing Practices, so that faults happening at various locations can be discovered in time and will arise. So that the entire batch will be preserved from becoming spoilt which as a result leads to saving time, labour, primary power, technology, and money. Making injectable hydrogels in accordance with quality by design is crucial, and doing so can be viewed as a successful choice.

Therefore, this review article's goal is to give readers a thorough grasp of the many facets of QbD while also addressing their worries about its implementation.

The following are the goals of this review-

1. Boost production effectiveness, cut expenses, project rejections
2. Create a scientific knowledge base for everyone
3. To Improve communication with industries upon businesses or on other scientific concerns
4. Reduce end-product testing, incorporate risk management
5. To provide consistent information about the QbD and its principles and also to accelerate release decision-making.

UNDERSTANDING QBD

a) Quality by Design is referred to as QbD. This methodical, scientific method to product creation and manufacturing places a strong emphasis on assuring product quality and complying with legal standards.

Understanding the effects of different factors on product quality, developing and regulating the manufacturing procedure in order to fulfil predetermined quality criteria, and continually observing and optimizing the process all over the course of the product lifecycle are all key components of QbD.

b) The fundamental tenet of QbD is to incorporate excellence into the product early on rather than depending exclusively on inspection and testing in the last stages. It incorporates a multidisciplinary strategy that combines information from several scientific fields, including engineering, data, and regulatory sciences as well as medicinal sciences.
c) QbD encourages the detection and management of risks early in the product creation procedure. It requires carefully defining your item's critical quality attributes (CQAs), determining the key critical process parameters (CPPs) which have an important influence on those characteristics, and creating a design space in which the process can operate while producing the ideal level of product quality consistently.
d) By using QbD ideas, manufacturers may gain a better understanding of the relationships between critical factors, conditions in the process, and product quality. This information enables the construction of robust control systems, continuous process monitoring, and aggressive risk management for consistent product quality and performance.
e) QbD is important not just for assuring product quality, but also for increasing process efficiency, decreasing variability, and improving patient safety. By delivering a thorough of science-based strategy for product development and manufacturing, it closely aligns with regulatory requirements and recommendations.
f) Overall, QbD represents an evolution in the pharmaceutical & biopharmaceutical sectors, with an emphasis on effectiveness, patient safety, or regulatory compliance across the product lifecycle. It promotes a risk-based, anticipatory approach to product creation, manufacture, and control.

WHAT ARE HYDROGELS OR INJECTABLE HYDROGELS?

Injectable hydrogels, also called hydrogels, which are a type of biological materials that may be supplied in liquid or gel state and then gel or solidify in the body after injection. These hydrogels are made up of a three-dimensional structure composed of hydrophilic polymers that can absorb and hold large amounts of water and biological fluids. Because of their unusual feature, they have a gel-like consistency and thus are suited for a variety of biological applications

Injectable hydrogels are divided into numerous categories depending on their composition, supply, and gelation process. Here are several examples:

1. Hydrogels Made from Natural Polymers: hydrogels are made with hyaluronic acid, a polysaccharide that exists naturally in the body. HA hydrogels are biocompatible and employed in a variety of biological applications.
2. Alginate hydrogels: these are produced from alginate, a seaweed polysaccharide. Alginate hydrogels create gel networks by ionic crosslinking, most often with calcium ions.
3. PEG Hydrogels: Polyethylene glycol, an artificial polymer, is used to make PEG hydrogels. These can be crosslinked via a variety of processes, including photo-crosslinking and chemical cross-linking.
4. PVA Hydrogels: PVA hydrogels are made using polyvinyl alcohol, also known as an artificial or synthetic polymer that is soluble in water. They can be crosslinked physically or chemically.
5. Hydrogels Made of Proteins: fibrin hydrogels are created by the enzyme-mediated breakdown of fibrinogen into fibrin and are obtained by fibrinogen, a component of blood plasma protein. They're frequently employed in the fields of tissue engineering & wound healing.
6. Collagen Hydrogels: Collagen hydro gels are made from collagen, a structural protein found throughout the body. They provide an environment similar to the ECM for encapsulating cells and tissue regeneration.
7. Hydrogels that respond to temperature: poloxamer hydrogels are hydrogels with thermos-responsive properties that go through a sol-gel transition when the temperature changes. They are able to be injected as a liquid and produce a gel on the spot.
8. Hydrogels Based on N-Isopropylacrylamide (NIPAAM): NIPAAM-based hydrogels have a lower critical temperature of the solution (LCST). When the temperature falls below their LCST, they gel.
9. Hydrogels that respond to pH: hydrogels of poly (acrylic acid) (PAA): PAA hydrogels have pH-responsive nature that can swell or Deswell depending on their surroundings. They are frequently employed in medication delivery applications.
10. Nanocomposite Hydrogels for Injection: injectable hydrogels may be coupled with nanoparticles, including gold nanoparticles and magnetic nanoparticles, to provide additional functions for image processing, sensing, or drug administration.

KEY POINTS OF QUALITY BY DESIGN IN THE INJECTABLE HYDROGELS

1. It is a tool for precise, flawless, and effective drug formulation and development
2. It is a modern and systematic approach with dynamic logistics
3. It depends upon the principle that Quality can be ensured by built-in processes
4. It is applicable to chemicals/biologics, drugs, drug processes, and upon drug product assessment.
5. It is applicable to the various analytical and theoretical methods
6. QbD can be implemented both partially or totally with ease to work and design
7. QbD can be implemented, referred to at any point and stage of process and formulation development
8. QbD is always encouraged and supported for Good Manufacturing Practices.

ADVANTAGES OF QBD

fig.2 advantages of QbD

1. The implementation of Quality by Design helps to eradicate the batch failures
2. It helps to standardize the fluctuating deviations
3. It also bypasses the expensive investigations
4. Quality by Design avoids regulatory complications
5. It helps in the strengthen of the staff of the pharmaceutical industry
6. It helps to reduce the cost of the final product
7. Provides flexibility and agility in the system
8. It makes a practical knowledge platform for all the products
9. Better interaction with regulatory authorities and between the pharma industries
10. consistent information flow is ensured
11. Eliminates the risk
12. Eliminate end-product quality testing.
13. Speed up the manufacturing process as post-manufacturing compliance is reduced.

METHODS AND KEY ELEMENTS OF QBD

1. Quality Target Product Profile (QTTP)

As part of the Quality by Design (QbD) methodology, the pharmaceutical sector uses QTTP idea. It is a methodical description of the qualities or qualities that a pharmacological product ought to have in order to achieve the specified therapeutic aims and guarantee patient safety. The QTTP is a resource for quality assurance, formulation design, process optimization, and product development. According to Quality Target Product Profile, the safety, effectiveness, and functionality of a medicinal product depend heavily on the QTTP, which is an extensive and established collection of quality criteria. It provides a clear aim for product development by describing the intended quality features in a quantitative and quantifiable manner. On the other hand, when the injectable hydrogels are concerned the QTTP lists the essential qualities (CQAs) an injectable hydrogel must have in order to fulfill its intended application, including stability, gelation time, viscosity, rate of release of drugs rate, and biocompatibility.

FEW HIGHLIGHTS TAKEN FROM QTTP

a) Patient-Centered: The QTTP is designed with the patient in mind, taking into account the intended usage, therapeutic aims, and patient needs. It considers dose form, mode of administration, distribution profile, equilibrium, appearance, flavor, and other product qualities that may influence patient acceptability and compliance.

b) Multidimensional Attributes Behavior: The QTTP includes a variety of quality parameters, such as the chemical, biological, physical, microbiological, and efficacy aspects of the medicinal product. Depending on the individual product and therapeutic requirements, these properties may include dose endurance, drug release description, dissolution rate, size of particles, content homogeneity, purity, strength, sterility, and others.

c) A risk-based approach: is used in the creation of QTTP to identify and prioritize essential quality criteria. Critical quality qualities are identified based on their possible impact on the product's safety, quality, and efficacy. A thorough risk assessment takes into account aspects including patient safety, legal requirements, scientific understanding, and the planned usage of the medicinal product.

d) Evolutionary Nature: QTTP development includes a risk-based evaluation. Nature's Evolution: The QTTP is not a permanent metric; rather, it can change during the product research lifecycle as additional data gets available or as knowledge of the product or patient requirements increases. It may be adjusted, updated, or enlarged in response to new scientific understanding, patient input, regulatory needs, or treatment aims that change.

e) Alignment with Regulatory Expectations or Requirements: The QTTP is in accordance with regulatory requirements and expectations for product quality as well as performance. It gives producers a clear aim for demonstrating and ensuring product quality, facilitating filings with regulators, and answering regulatory concerns during the approval process.

Cause here: / Effect on:		Product Development	Decomposition	Disciplines & Technologies	Product Life	Synthesis Matrix	Life phase systems	Goal/Results	Tasks	Activities/Plan	Resources	Design history
		1	2	3	4	5	6	7	8	9	10	11
Product Development	1	X	X	X	X	X	X	X	X	X	X	
Decomposition	2		X	X	X	X	X	X	X	X	X	
Disciplines & Technologies	3		X			X		X	X	X	X	
Product Life	4			X	X	X	X	X	X	X	X	
Synthesis Matrix	5		X		X	X	X	X		X	X	
Life phase systems	6						X	X		X	X	
Goal/Results	7			X	X	X				X	X	
Tasks	8	X		X	X			X	X	X	X	
Activities/Plan	9							X	X	X	X	
Resources	10	X		X				X	X	X		
Design History	11											

fig.3 different aspects of quality target product profile (QTPP)

2. DESIGN SPACE

The multidimensional assortment of input factors (such as formulation composition and process variables) that determine whether a product can consistently fulfil the intended quality characteristics is known as the design space and is a fundamental idea for Quality by Design (QbD). It represents the permissible limits or ranges of these factors that may be investigated throughout the design and production of a product while maintaining the target product quality.

Multiple factors that are essential to product quality are included in the design space, which is multidimensional in nature. Aspects of the raw materials, the makeup of the formulation, the processing parameters (such as temperature, time, and pressure), including equipment settings are a few examples of these variables.

a) Flexible yet Controlled: The realm of design allows manufacturers to modify and improve the formulation as well as the parameters as long as they stay within the predetermined bounds. This adaptability allows for ongoing process improvement, innovation, and product performance while guaranteeing product quality.
b) Risk-Based Approach: The creation of an environment for design is based upon a risk-based approach that takes into account how many factors may affect the quality of the final product and patient safety. In order to estimate the risks, any modifications in the formulation and process parameters in the design space must be identified.
c) Verification & Control Strategy: Following the establishment of the design space, a strong control strategy ought to be created to make absolutely certain the process keeps to the boundaries that have been set. This control technique involves installing suitable procedure controls, in-process testing, and overall control procedures as well as monitoring and regulating the most important (CPPs) & (CQAs).

3. Critical Quality Attribute (CQAS)

This step comes after the identification of the Quality Target Product Profile (QTTP)

Critical Quality Attribute may be 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"

FOLLOWING POINTS ABOUT CRITICAL QUALITY ATTRIBUTE.

I. CQAs are mainly linked with raw materials such as excipient, drug, drug substance, their respective intermediates, and drug product.
II. CQAs are those properties that are most important for product reliability and performance, it implies towards the desired efficacy safety, and quality of the product.
III. CQAs are subspace of the all the QTPP's which has a huge tendency to be modifies and altered by the change in methods, formulation and in the different process attributes.

For instance, Quality Target Product Profile includes additional or surplus quality standards and attributes of the respective drug product like as physical strength and dosage form, which are practically not the fragment of Critical Quality Attributes as they will remain unchanged during the whole drug formulation process. However, various QTTP accredit such as dissolution, uniformity of the content, and flux permeation will also be an integral part of CQA as they are reliable to get altered by any process variables regarding the methodology and Identification of Critical Quality Attributes are made through risk judgment as per the ICH Q9 guidance. The essential factor in conducting risk assessments is being familiar with a product in advance, which includes knowledge of laboratory investigations, preclinical or clinical experiments, and analysing specific aspects linked to product quality. This comprehension can include knowledge gathered from analogous substances as well as literary references. By combining this knowledge, a reasonable basis is created for understanding the link between Critical Quality Attributes (CQA) as well as the greater safety and efficacy of the product. Drug loading, drug absorption motion, mechanical strength, gelation kinetics, and compliance with the target tissue and organ are only a few CQAs for injectable hydrogels.

CQA examples vary based on the product, however, they may include:

1. The concentration or dose of the active medicinal ingredient (API) contained in the product is referred to as its potency or strength. It is critical to guarantee that the product has the desired therapeutic impact.
2. Purity refers to the presence or restricted presence of contaminants, such as additional chemicals or pollutants, that might possibly compromise the product's safety or efficacy.
3. Stability is important. CQAs evaluate a product's capacity to preserve its quality and efficacy over time, taking into account aspects such as deterioration, its shelf life, and conditions of storage.
4. Dissolution rate indicates how quickly the substance dissolves in the human body, ensuring maximum absorption and effectiveness for oral dose forms.
5. The homogeneity, solubility, and flow qualities of goods in particulate form, including powders or suspensions, are all impacted by the particle size distribution.
6. In order to maintain patient safety, sterile items must be free of bacteria or other microbial contaminants.
7. The amount and pace which the active component is taken in by the human body have an impact on its curative effect and efficacy, which is referred to as bioavailability.
8. Container closure reliability: This characteristic evaluates how well the product's container is sealed and shielded from outside pollutants or moisture.

Critical quality attribute (risk level):	Unit operations							
	Preculture & expansion	Fermen-tation and harvest	Centri-fugation	Cation exchange chroma-tography	Anion exchange chroma-tography	Viral filtration	Concen-tration & dia-filtration	Vial filling
Appearance (M)	Low	Low	Medium	No	No	Low	Low	Low
Impurities (H)	Medium	High	Medium	High	High	Medium	Low	Low
Protein content (H)	Low	High	Medium	Medium	Medium	Low	Medium	No
Immunoreactivity (H)	Low	Medium	Low	Low	Low	Low	Low	No
Purity (H)	Low	Low	Low	Medium	Medium	Medium	Low	No
pH and ionic strength (M)	Low	Low	No	Low	Low	Low	Medium	No
Amino acid content/ratio (H)	Medium	Low	No	Low	Low	No	No	No
Bioburden (H)	Low	Low	No	High	High	Medium	Medium	Low
In-process controls								
Fill weight check (M)	No	No	No	No	No	No	No	High
Visual inspection (M, L)	No	No	Medium	No	No	Low	Low	Medium

fig.4 critical quality attributes unit operations

4. QUALITY RISK MANAGEMENT (QRM)

In order to guarantee both the quality of the final product and the safety of the patient, Quality Risk Management provides an essential aspect of the Quality by Design (QbD) concepts. QRM is a methodical procedure used to recognize, evaluate, manage, communicate, or review risks related to the development, production, and distribution of pharmaceuticals. Components for Quality Risk Management within QbD include the following:

a) Risk Assessment: A systematic and thorough risk assessment is the first step in QRM. This entails identifying possible hazards, assessing their likelihood and seriousness, and determining how they may affect the effectiveness, efficacy, & patient safety of the product. Risk assessment may be supported by a number of methods and methodologies, including Hazardous Material Analysis or Critical Control Points (HACCP), and Fault Tree Analysis (FTA).

b) Risk Identification: Throughout the whole product lifetime, including formulation creation, manufacturing procedures, packaging, labeling, storage, transportation, and usage, QRM strives to detect both known and prospective dangers. This entails taking into account all elements that may have an influence on the quality of the final product, including the environment, raw materials, tools, and staff.

c) Risk Evaluation: The relevance or the priority of every danger is determined by a qualitative and quantitative appraisal that follows the identification of hazards. Aspects including severity, likelihood of their occurrence, detectability, and influence on key quality attributes (CQAs) & the critical parameters of the process may be taken into account during the evaluation.

d) Risk Control: To reduce or completely eliminate recognized hazards, risk management methods are created and put into practice. In order to do this, it may be necessary to install suitable process controls, employ validated analytical techniques, create specifications, include process analytical tools (PAT), carry out in-process monitoring, and put containment measures in place.

e) Risk communication: In order to ensure that key stakeholders, including regulatory agencies, are informed of possible hazards and suitable risk mitigation techniques, successful risk outreach is essential. To enable rapid, transparent, and unambiguous decision-making, communication is essential.

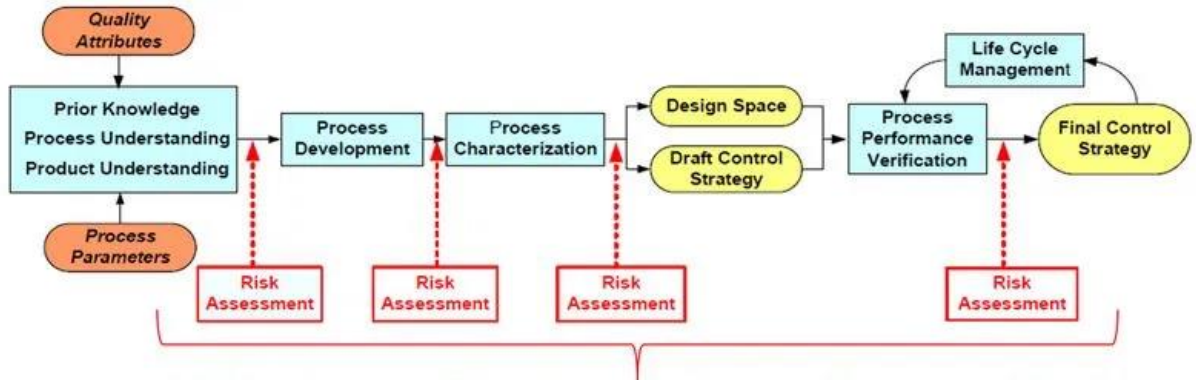

fig.5 quality risk management (QRM) at every stage throughout the development lifecycle

5. CRITICAL MATERIAL ATTRIBUTES

Critical material attributes (CMAs) as well as critical process parameters (CPPs) both are chosen for the creation of injectable hydrogels. CMAs are raw material characteristics that can affect CQAs, including polymer type, molecular size, quantity, cross-linking agent type, and drug properties. CPPs are the process variables that affect the creation and characteristics of the injectable hydrogel, such as mixing rate, temperature, pH, and linking conditions.

6. CONTROL STRATEGY

The control strategy is an essential component of Quality by Design (QbD) in the pharmaceutical and biotechnology industries. It entails the protocols and safeguards applied to control crucial process parameters (CPPs), crucial material characteristics, and other factors that have a significant impact on product quality. The goal of the control plan is to ensure that the product consistently satisfies the stated key quality characteristics (CQAs) and regulatory requirements. Building a strong control plan starts with having a firm understanding of the product & procedure through scientific research, risk analysis, and testing. The control method focuses on putting in place appropriate controls as well as monitoring systems to reduce risks and ensure constant good quality by identifying key elements and potential sources of variability. The control strategy includes a variety of components such as in-process oversight, process surveillance, and testing procedures. In-process controls comprise monitoring and reviewing critical metrics at various stages of the manufacturing process in order to discover and rectify any irregularities as soon as possible. These controls include checks on raw materials, apparatus calibration, surroundings, and intermediate manufacturing steps, to name a few. Process monitoring, which allows for in-process evaluation and change in the manufacturing process, is a vital aspect of the control strategy. Critical parameters related to the process are regularly checked to ensure that they are within predefined limits as well as the process is operating under verified conditions. This continuous monitoring is enabled by advanced procedure analytical technology and continuous monitoring systems, which also allow for rapid action to halt. Testing techniques are required for ensuring product excellence and compliance with CQAs. An established testing regime that includes both in-process and final product testing is part of the control approach. In-process testing ensures that quality requirements are met throughout the production process. Finished product testing is a thorough examination to ensure that the product fulfills all essential requirements, such as identification, effectiveness, purity, dissolution, and durability. The control approach is dynamic, developing depending on the information obtained through process comprehension, data analysis, and continuous improvement activities. It entails reviewing and reassessing control measures on a regular basis to guarantee their efficacy and applicability. This iterative approach aids in the identification of possibilities for process improvement, risk mitigation, and optimization. All essential stakeholders, including production staff, assurance of quality teams, regulatory agencies, and other important individuals who participate in the product lifecycle, are provided with a thorough control strategy that is recorded and disseminated. This guarantees that the control measures are understood by everyone and allows for uniform application across multiple manufacturing sites or batches. Overall, a major part of QbD is the control strategy, which aims to provide a systematic and based-on-science approach to controlling critical variables, mitigating risks, and maintaining the quality of the product throughout its lifespan. Pharmaceutical and biopharmaceutical firms may improve process robustness, minimize variability, and assure the manufacturing of safe and effective products that satisfy patient demands and regulatory standards by implementing a successful monitoring plan.

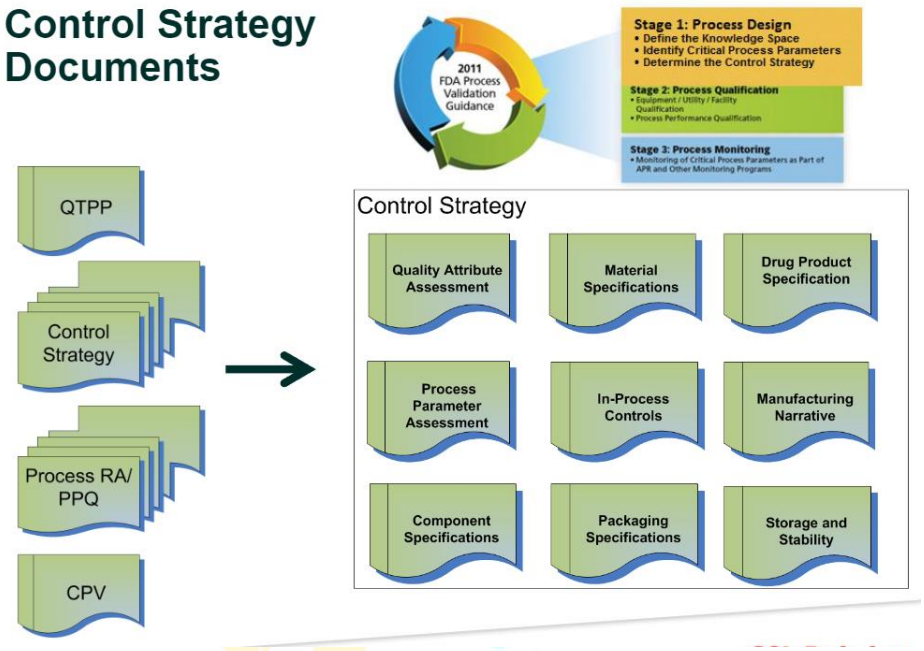

fig.6 documentation of control strategy.

7. **CONTINUOUS PROCESS VERIFICATION (CPV)**
   CPV entails constant evaluation and monitoring of process data in order to make sure that the process is kept under control and that the product consistently satisfies the established quality criteria. In order to spot any variations or potential dangers, it involves trending, periodic evaluation, and real-time monitoring.
8. **KNOWLEDGE MANAGEMENT**
   QbD emphasizes the need to carefully obtain, analyze, and implement knowledge gathered during product development and manufacturing. This includes formulation enhancement, process understanding, and data-driven insights. Effective knowledge management ensures continuous development while also making decisions easier throughout the product's lifecycle.

RESULTS

1. The use of Quality by Design (QbD) has produced a number of positive outcomes within the pharmacy and biopharmaceutical industries. Here are some significant results and advantages of applying QbD principles:
2. Product Quality Improvement: QbD emphasizes an aggressive, analytical approach to product creation and manufacturing. QbD has enhanced the consistency and quality of products by focusing on understanding and managing critical factors. Critical Quality Attributes (CQAs) need to be established and monitored consistently to ensure that commodities meet predetermined quality criteria and exhibit acceptable performance characteristics.
3. Increased Process Understanding: QbD enhances extensive process understanding through the use of risk examinations, design of experiments (DoE), and statistical analysis. This technique has resulted in a better knowledge of the procedure or product, including the impact of significant elements and the causes of variability. As a result, manufacturers now have in-depth understanding of how they operate that will aid with leadership and optimization.
4. Product Variability Reduction: By identifying and regulating key process parameters (CPPs) and critical material attributes (CMAs), QbD was able to reduce product variability. Processes with narrower control ranges may be designed by manufacturers, resulting in less fluctuation in product quality. This has important consequences for completing regulatory standards and ensuring patients receive consistent therapy effects.
5. Risk Reduction and Increased Safety: Risk assessment is a key aspect of the product creation procedure in QbD. This thorough assessment of possible threats to the health of patients and product quality enables the deployment of suitable control measures. QbD has helped to enhanced safety profiles and lowered the chance of adverse events by addressing possible concerns prior to the development stages.
6. Manufacturing that is efficient and economical is facilitated by the implementation of QbD concepts. Manufacturers may optimize processes and reduce waste by recognizing the impact of crucial variables and concentrating on managing those that have the most impact on product quality. As a result, operational effectiveness is increased, and resources, assets, and time are all saved.

7. Encourages Regulatory Compliance: QbD closely complies with regulatory requirements and standards, especially those that place a focus on a risk-based strategy for product creation and manufacturing. By putting QbD concepts into practise, manufacturers are better able to support regulatory filings with solid data and proof that they have a thorough grasp of their goods and processes. This promotes a quicker speed to market and helps the regulatory clearance process run more smoothly.
8. Lifecycle Management and Continuous Improvement: QbD encourages a culture of lifecycle management and continuous improvement. Manufacturers can find chances for process improvement, risk reduction, and optimization through ongoing surveillance, data analysis, and loops of feedback. This makes it possible for businesses to adopt new technology, take advantage of shifting market dynamics, and sustain product quality over time.
9. Overall, both the pharmaceutical or biopharmaceutical sectors have benefited directly from the introduction of QbD. It has boosted productivity, decreased risks, expanded process understanding, and improved product quality. Firms have a stronger chance to offer high-quality, safe, and effective goods while adhering to regulatory standards and retaining an edge in their sector by adopting QbD principles.
10. As part of this, acceptability criteria must be established, requirements for the beginning materials and final goods must be established, process controls must be put into place, and suitable analytical techniques must be developed for monitoring and evaluating the injectable hydrogel qualities.

CHALLENGES

As it is well known that Quality by Design is a very essential part of ensuring quality towards the modern approach and also in the case of injectable hydrogel preparations with other pharmaceutical preparations too, but when injectable hydrogel preparations are concerned, they are parental dosage forms which are meant to get incorporated directly into the main bloodstream to provide the fast, efficient onset action of the drug in less amount of time. But there are some reasons why QBD is to still very difficult to implement. There are many different challenges behind this, out of which some of the main reasons are mentioned here,

The following are primary reasons which are obstructing the implementation of Quality by Design are as follows

- Misunderstanding of the facts and guidelines: most pharmaceutical companies feel that there is still a requirement for some easily understandable guidance document with some easily operable methods to implement the standards of Quality by Design, out of which some companies and some pharmacy industries are confused till today either to adopt and implement the standards of Quality by Design or not or either it would be profitable or not.
- FDA: many of the pharmaceutical industries have an opinion that the FDA should fix a standard that how to implement the concept of QbD regarding its terminologies and the processes and procedures mentioned.
- Confusion between different regulatory departments with the pharma companies: diverse departments within a pharmaceutical corporation handle diverse responsibilities like production, quality assurance, packing, handling, etc. However, it has frequently been pointed out that these departments are connected, which frequently results in misunderstandings in these areas. No department is explicitly told what task to do or which Critical Quality Attribute to apply. Comparatively, when regulatory agencies are taken into account, these departments find it difficult to determine what should be done and what should not be done as a result of these sorts of mismanagement. When it comes to the export and import of drugs, the department's problems are most noticeable. As the essential characteristics of quality in the region or nation that manufacturing zone is distinct, and the location where the preparation is being made available for consumption has certain additional crucial characteristics due to which the problem arises.
- Only focus on the end product rather than on the whole process: despite the entire procedure, all pharmaceutical companies that make pharmaceuticals have concentrated solely on the formation of the end product first and after that screening. After the product is made, it is subjected to a number of quality control tests, and when the preparation fails during screening, the batch is discarded. In order to avoid failure in the end, none of the manufacturers bother to approach the multistep QC beforehand and during the process.
- Lack of communication between the pharmaceutical companies: one of the main reasons is a technical deficiency, due to which there are gaps in data management and technical terminology. Lack of understanding is the biggest reason why the main challenges are hindering the way of Quality by Design.

CONCLUSION

In conclusion, the pharmaceutical & biopharmaceutical sectors have seen substantial gains as a result of the introduction in Quality by Design (QbD). By placing a strong emphasis on an innovative and science-based process, QbD has

revolutionized the conventional approach to product creation and manufacturing. QbD has revolutionized how goods are created, regulated, and manufactured by merging scientific knowledge, assessment of risk, and data-driven methodologies. This has contributed to the quality of the product, patient safety, and compliance with regulations. As it is a well-known fact that the pharmaceutical sector still has numerous process and production defects. This entire study demonstrates that Quality by Design is a tool that the pharmaceutical industry is currently pursuing, and from the above study, it is stated that it can be a practical, affordable solution for injectable hydrogen preparation as well as for every pharmaceutical preparation respectively. If the injectable hydrogels can be screened by the method of QBD It could be proven to be a turning point for injectable hydrogel formulations in the future.

This study reveals the following observations

1. That from prior manufacturing if a proper outline of the necessary documentation, selection of process, selection, and identification of critical quality attributes is done then as a result we may avoid many of the current emerging problems and challenges.
2. Because of QbD, manufacturers have a greater understanding of their goods and processes, allowing them to identify and control critical elements that impact product quality. Because of a greater understanding of the process, production techniques have been improved, and product volatility has been decreased. Manufacturers have been able to ensure that items meet specified critical quality attributes (CQAs) and legislative requirements on a continual basis by using stringent control systems such as during production controls, process surveillance, and testing processes.
3. QbD has also improved risk reduction by incorporating risk assessment as an important element of the development process. Manufacturers can use appropriate control methods to limit the likelihood of complications and ensure patient safety by discovering and resolving potential dangers early prior to any manufacturing. Overall, the deployment of QbD has transformed the pharmaceutical & biopharmaceutical businesses. It has improved product quality, process understanding, risk minimization, cost-effective production, and patient safety. Companies that embrace QbD concepts are better positioned to offer secure, efficient, and high-quality goods, allowing them to maintain a competitive advantage in the global market while satisfying patients' shifting requirements and regulatory expectations.
4. The development and manufacture of injectable hydrogels may be made more methodical, science-based, and risk-controlled by utilizing QbD principles. QbD guarantees that high-quality material is incorporated into the formulation & process, resulting in consistent and dependable injectable hydrogel performance from discovery to use.

Acknowledgment

First and foremost, I bow before the Almighty for showering his blessings on me without which I would have not reached this stage. I thank Almighty in these blissful moments and mercifulness to allow me to finalize this review paper and research.

This research was successfully achieved through the cooperation of many individuals. First of all, I would like to express my appreciation to my major advisor, "**Prof. Ankita Pokhriyal.** Associate Professor GRD Institute of Management and Technology Rajpur Road, Dehradun, Uttarakhand for her encouragement, patience, valuable comments, and support given throughout my time in this research.

An appreciation is extended to all my teaching and nonteaching staff of the institute with all my fellow friends.

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