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REVIEW ARTICLE

Quality by design – A Systematic Approach to Enhance Quality Matrix

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ABSTRACT

Quality by design is utilized by the pharmaceutical industry to achieve quality products. This approach focuses on designing and developing products and processes to ensure predefined quality. It is a science-based approach that reduces product variation and enables process control strategies, improving process reliability and understanding. It is considered the sensible approach to minimizing batch failures, deviations, and expensive investigations. Quality by design (QbD) elements include quality target product profile, critical quality attributes, critical material attributes, critical process parameters, a control strategy that includes specifications for the drug substance(s), excipient(s), and process capability and continual improvement. Thus, the QbD is a modern approach to developing an effective and quality pharmaceutical product.

Keywords: Advantages, Continual improvement, Modern approach, QbD elements, Quality

INTRODUCTION

The pharmaceutical company's mission is to create and innovate high-quality products. The pharmaceutical industry works tirelessly to promote and guarantee the safety, quality, and effectiveness of the product. nevertheless, contemporary industry challenges include burden, production failures, expense, scale-up concerns, and medication recall. Conventionally, the completed product assessment unit, which has a limited grasp of the process and key process parameters (CPPs), verifies product quality and performance. As a result, regulatory organizations are concentrating on implementation through quality by design (QbD). QbD is a science-based strategy that leads to better process knowledge and dependability by reducing process variance and allowing process control measures**.** QbD is a science-based strategy that leads to better process knowledge and dependability by reducing process variance and allowing process control measures. We do not need to QbD promotes openness across the whole development process, reducing the reliance on final product testing alone and enabling effective analysis of quality concerns as well as the speedy identification and resolution of underlying issues. Identifying the potential influence of any modifications on the quality of the end product is a QbD requirement. Moreover, all crucial formulation characteristics and associated process parameters must be identified.[1]

Definition (Q8 [R1] of the international conference on harmonization [ICH]) is a methodical strategy for creating that starts with a predetermined objective and places an emphasis on methodology and product, management of methodology and

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understanding, underpinned by strong science, and quality risk management (QRM).

Definition (according to the Food and Drug Administration Process Analytical Technology [FDA PAT] rules) is a method for planning, studying, and controlling production and the construction of bounding final product safety by timely measurements (that is, during processing) of essential quality and performance attributes of new and in-process materials and processes. Because of the contemporary approach to the creation of essential methodologies and the quality product supported knowledge base across the event sector of the merchandise, QbD concept was printed.[2]

BACKGROUND AND HISTORY

Dr. Joseph M. Juran, a pioneer in the development of standards, proposed the concept of quality purposefully (QbD), which suggests that quality should be planned for quality in a product, with the majority of quality problems stemming from how the product was initially created. Being a product free from contamination and faithfully delivering the therapeutic benefit guaranteed on the label to the customer, the Limicoline bird is without a doubt a high-quality drug product.

A new risk management effort was launched by a government agency in 2002 (cGMP for the 21st century: A risk-based mostly approach). As a result, the FDA's control of pharmaceutical quality began to be modernized i.e. starting a new regulatory framework that is backed by a QbD quality and risk management system. Two papers, ICH-Q8 (for pharmaceutical development) and ICH-Q9 (for guiding the standard), were introduced by the ICH to support this more recent FDA-cGMP initiative (QRM). The pharmaceutical industry has a great deal of leeway in the twenty-first century to offer new concepts, innovations, and improvements that will improve quality, cost, or timing.[3]

BENEFITS OF QBD

The concept of "QbD" is defined as an approach that entails a more in-depth scientific comprehension of critical processes and product attributes. It involves creating controls and tests rooted in the scientific boundaries of understanding during the development phase and utilizing the knowledge acquired throughout the product's lifecycle to foster a continuous improvement environment. QbD encompasses a pharmaceutical development methodology related to formulation design, development, and manufacturing processes to uphold the specified product quality. Guidelines and mathematical models are employed to guarantee the establishment and application of knowledge on the subject in a self-reliant and cohesive manner. Some benefits of QbD are listed below in Table 1.[4]

ADVANTAGES OF QBD

QbD may be a smart company strategy that reduces costly research, batch failures, and deviations. QbD

Table 1: Benefits of quality by design[5]

S. No	Benefits of QbD	
	From a business perspective	
1.	Eliminates batch failures	QbD helps in preventing batch failures, reducing wastage, and ensuring a more consistent product quality
2.	Minimizes deviations and costly investigations	By design, QbD reduces the likelihood of deviations and the need for expensive and time-consuming investigations, thus saving resources.
3.	Avoids regulatory compliance problems	Adhering to QbD principles helps maintain regulatory compliance, avoiding potential issues and penalties.
4.	Organizational learning is an investment in the future	Through QbD, organizations can cultivate a culture of continuous improvement and learning, which is an investment in their long-term success.
	From a scientific perspective	
5.	Better development decisions	QbD facilitates better decision-making in the development process, as it is based on a deep understanding of critical factors and their impact on product quality.
6.	Empowerment of technical staff	It empowers technical staff by providing them with the tools and knowledge to make informed decisions and contribute to product quality improvement.

further stays away from regulation compliance difficulties and structural learning may warrant future investment. Ultimately, QbD is a sweet science that provides technical staff management and greater development options. The QbD technology is affordable, quick, and adaptable. It creates a knowledge domain, guarantees consistent information, and greatly improves risk management, principally for all goods. These edges increase the generating potency and decrease the producing value. ICH Q10 outlines a model for the establishment of an effective quality management system that will be used by manufacturers employing QbD systems and may help them value and enhance product quality during the product's lifetime.[6,7]

PRINCIPLES OF QBD

These components of a QbD development strategy are:

1. The target product profile (TPP) should be shaped because the association between effectiveness, safety, and quality is achieved. Identifying the product's standard features will serve as the foundation for its development and planning.
2. Identify crucial quality factors (critical quality attributes [CQAs]): Key quality attributes are the product's material characteristics that must fall within their accepted ranges, limitations, or distribution to provide the desired level of product quality and methods of change management.
3. Risk assessment comparison of material features and CPPs to CQAs. The CPPs will be determined using risk assessment techniques such as failure mode and effects analysis (FMEA) or bone diagrams. The instruments that will be used are listed in ICH Q9 in the method for managing changes.
4. With the use of a style of experiments (DOEs), a relationship and significant interaction between CPPs and CQAs may be developed and very effectively reflected in the establishment of a space design esthetic field.
5. Management plan is necessary to recognize, comprehend, and manage or control significant sources of unpredictability.[8,9]
6. Product lifecycle management and ongoing development as described in [Figure 1].

TPP

TPP defines the needed profile or qualities of a drug product for drug labeling and drug development operations. TPP indicates intended use, target, administration speed, and other important product qualities, as well as quality design for a pharmacological product.

Target quality product profile (TQPP)

TQPP is a possible logical extension of TPP for product quality. The quality target product profile (QTPP) is an important document that provides for rationalization and harmonization. Tracking the evolution of the data is not inheritable over the drug's lifespan. "To affirm the targeted quality a prospective outline of the quality attributes for a drug product that is going to be accomplished and taking into mind the target product's safety and efficacy." TQPP encompasses indefinite-quantity, type, indefinite-quantity, strength, instrumentation closure system, identity, and purity.

CQA

CQAs are physical, biological, microbiological, and chemical characteristics that ensure the product obtained will meet the intended quality, safety, effectiveness, and stability. This can also be defined, measured, and regularly monitored to ensure that final product outputs are within acceptable quality norms. Quality characteristics include clinical safety and efficacy, manufacturing an attribute, and parameter boundaries approach

Figure 1: Components of QbD

edge of failure, the criticality of the APT manufacturing process may change, and the number of criticality increases in risk.

Critical material attributes (CMAs)

A parameter is significant when a real change in that parameter causes the product to fail to meet the QTPP. As a result, whether or not a parameter is significant or not depends on how much of an alteration one is ready to consider, as well as other attributes or characteristics of associated input material. To ensure the appropriate quality of that drug ingredient, excipient, or in-process material, CMAs should be within the associated applicable limit, range, or distribution.

Critical process parameters (CPP)

Every quantifiable input (input material characteristics or operational parameter) or output (process state variable or output) is defined as CPP. A characteristic of a procedure that needs to be controlled is to attain the intended product quality and process consistency. Each item in this read would be a method parameter. Parameters are checked before or during procedures that significantly impact the appearance, impurity, and yield of the final product.[10]

Risk assessment

Risk is the product of the likelihood of injury and the severity of that injury. Risk assessment contributes to the improvement of product quality, technique, or procedure. A risk assessment will identify critical qualities that influence the overall quality of the product. A risk assessment is useful for good communication between the FDA and trades, research/development, and manufacturing, as well as across numerous manufacturing locations throughout the corporation. Techniques for assessing risk: Several risk assessment square measure methodologies described in ICH guideline Q9 are given in [Figure 2].[11]

FMEA

FMEA is one of the most often utilized risk-assessment methodologies for identifying

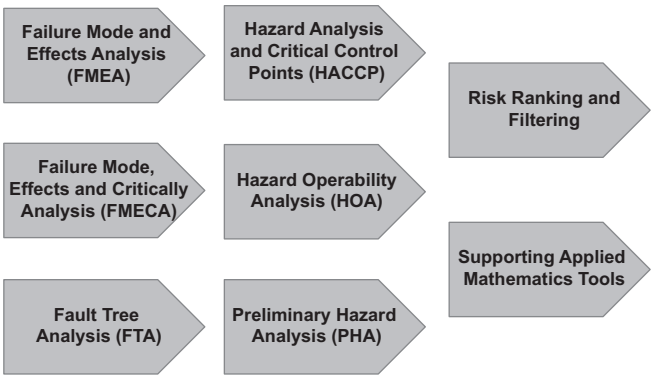

Figure 2: Risk assessment methodologies as per ICH 9 guidelines

and minimizing possible process failures in pharmaceutical industries. It is a scientific and proactive approach to identify any faults or deficiencies in an excessive process, material, design, or instrumentality pictured\sin failure mode. Once the failure modes and square measure have been determined, the FMEA tool assesses the outcome of those failures and prioritizes them accordingly. This tool is more complex, with the ability to understand the criticality of the findings and provide a clear indicator of the state of things.

Failure mode, effects, and critical analysis (FMECA)

It is the addition of the previously described FMEA tool. Expanding the independent agency's probe to encompass the failure mode, effects, and criticality analysis determines the severity of the repercussions, their likelihood of occurrence, and detectability. Every failure mechanism of the goods is known in FMECA, and thus, the criticality of the situation is assessed. This criticality becomes a risk, and if the amount of risk is unacceptable, corrective action should be performed. This might be utilized for failure and risk in manufacturing operations. The tool may also be used to create and optimize maintenance plans for operational systems, as well as to contribute to regulatory planning and various quality assurance procedures.

Fault tree analysis

This tool assumes that a product or method's practicability has failed- results in the square

measure depicted pictorially within the context of a tree and various fault modes. It may be necessary to examine complaints or deviations to determine their core cause and ensure that proposed improvements would fix issues while not causing new ones.

Hazard analysis and critical control points (HACCP)

To command and supervise HACCP offers meticulous documentation to demonstrate procedure or product comprehension via separate factors. The term danger encompasses both safety and quality. Hence, worry about an exceeding method or product. It entails hazard analysis, deciding on essential management goals, creating important boundaries, developing a method to monitor critical management goals, and establishing a record-keeping system.[12,13]

Design space

It is the multidimensional combination and interplay of input variables (for example, material qualities) and process parameters that ensure quality. It is decided to leave the planned area considered to be a modification and would typically commence a limited post-approval amendment process. The individual creates the planning area, which is subject to careful examination and approval. The region might be a Y (Quality Attributes) = F (Process Parameters Material Attributes) – a function or connection between (critical) procedure parameters and (critical) quality attributes/material characteristics for the scientist. This concept refers to a multidimensional combination and interaction of input variables and process parameters that have been shown to deliver quality assurance. This is often represented in a visual format as shown in [Figure 3], illustrating how various factors come together and influence the assurance of product quality. It highlights that quality assurance is not the result of a single factor but rather the intricate interplay of multiple variables and parameters within a process or system.[14]

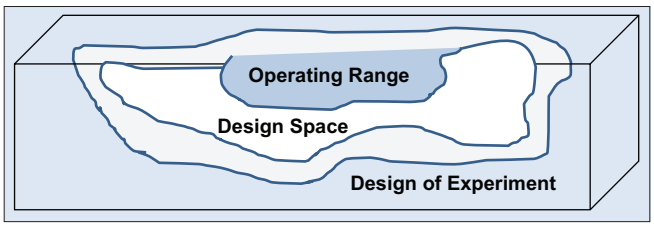

Figure 3: Design space

Strategy for control

To ensure that the stated quality product meets raw material criteria, an effective plan should be established and managed. Method controls, in-method testing, and final product testing are all examples of quality assurance. This approach identifies critical method parameters as well as essential material properties. PAT is frequently employed for this reason, which will eventually be scaled back depending on the type of house to maintain quality. The components of a successful strategy are described in [Figure 4]. The management approach within the QbD commonplace is formed by risk assessment, which takes the criticality of the CQAs into account.[15]

Product shelf-life management and continuous improvement

Product quality is frequently upgraded throughout the product's lifetime; businesses can adopt inventive techniques to increase quality. Procedure performance is often checked to ensure quality consistency. During ordinary manufacturing,

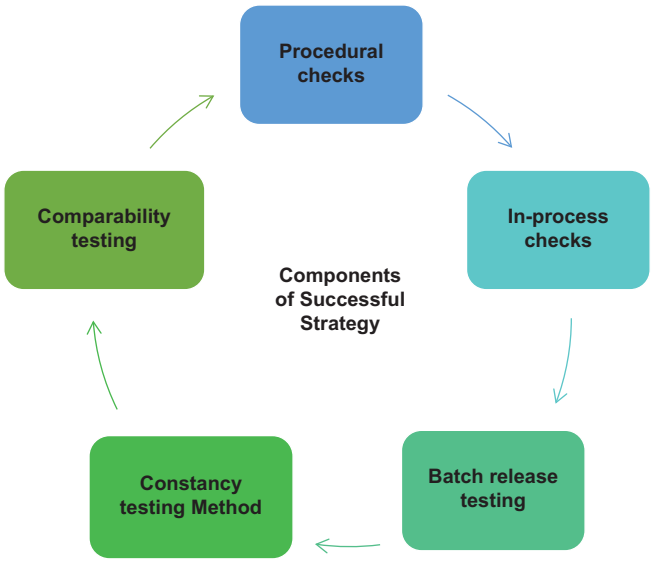

Figure 4: Components of successful strategy

additional experience and information are gathered, which adds to method/process development. Frequent maintenance of a company's internal quality system is common; nonetheless, the style area should remain intact. The QbD methodology allows for continuous improvement throughout the product's lifespan, which is a feature of the conventional process, which is the manner frozen method.[16]

PAT

The US FDA created PAT as a tool to vogue, evaluate, and regulate pharmaceutical production procedures. CPP activity influences key quality aspects (CQAs). The idea is to comprehend the processes of molding their CPPs and, as a result, observe them in a timely manner (ideally in-line or online) and therefore be plenty economical in testing while lowering over-processing, improving uniformity, and minimizing rejections. The administration has made a limiting framework for PAT implementation public.

PAT is a word used to describe a larger change in pharmaceutical manufacturing from static batch production to a variety of dynamic alternatives. It entails processing the instrumentation's CPPs accustomed, to creating the product, which has an effect on the product's CQAs and thus, dominates these CPPs at intervals outlined limits. This allows manufacturers to provide products of consistent quality while also reducing waste and overall costs. This mechanism for producing consistent product quality while reducing waste makes a compelling case for utilizing continuous manufacturing technologies. The management of a gentle state method is a simpler task once you understand the upstream and downstream effects because common cause variability is easier to define and monitor.[1]

PAT TOOLS

To apply a productive PAT project, a mixture of 3 main PAT tools is essential: Multivariate knowledge acquisition and knowledge analysis tools: In general, complex software packages, programs that help in the design of ex programs an assortment of raw data, and statistical evaluating this data to determine which parameters are significant. Process analytical chemistry tools: CPP parameters are used by in-line and online analysis tools. They include, first and foremost, near-infrared spectroscopy, but furthermore biosensors, Raman spectrometry, and fiber optics.[17]

QBD IN PHARMACEUTICAL INDUSTRIES

While the pharmaceutical industry has traditionally placed a strong emphasis on quality, it has not managed to match the manufacturing efficiency and productivity levels seen in other industries. Here is a summary of the current scenario in the pharmaceutical industry and the need for a systematic approach to development.[17]

Current status in the pharmaceutical industry

- Cost of revalidation: Revalidation processes come with significant costs and efforts.
- Off-line analysis for in-process-need based: In-process analysis often relies on offline methods, which can be time-consuming and may not be performed in real-time as needed.
- Product specifications as the primary means of control: Product specifications play a central role in quality control, but they may not cover all aspects of process control adequately.
- Unpredictable Scale-up issues: Scaling up production from small to large scale can present unexpected challenges and issues.
- Inability to understand failures: Failures or deviations in the manufacturing process are not always well-understood, leading to inefficiencies and quality issues.[18]

Systematic approach to development

A systematic approach to development is required, which:

- Begins with pre-defined objectives: Having clear, predefined objectives for product development is essential to ensure a well-structured process.
- Emphasizes products and process understanding: Understanding the products

and the underlying processes is crucial for maintaining consistent quality and efficiency.
- Prioritizes process control: A focus on process control ensures that manufacturing is predictable and deviations are minimized, leading to higher efficiency and productivity.

The pharmaceutical industry faces challenges in terms of manufacturing efficiency and productivity, with issues related to revalidation costs, in-process analysis, and understanding failures. To address these challenges, adopting a systematic approach that begins with clear objectives, emphasizes product and process understanding, and prioritizes process control is essential.[19]

The benefits of implementing QbD for the (U.S. FDA) include

- Enhancing the scientific foundation for review: QbD provides a more robust and scientifically driven framework for the FDA's review process. It promotes a deeper understanding of critical factors, process control, and product quality, which can lead to more informed and efficient evaluations of pharmaceutical products. It is important to note that QbD offers several other advantages for both the pharmaceutical industry and regulatory agencies, such as improved product quality, reduced batch failures, and greater regulatory compliance.
- The benefits of implementing QbD for both regulatory agencies and the pharmaceutical industry are described in [Tables 2 and 3].[20]

The adoption of QbD benefits regulatory agencies by enhancing coordination, improving regulatory submissions, and ensuring science-based decisions, while the pharmaceutical industry gains advantages such as improved product design, cost reduction, and a more efficient regulatory process.

APPLICATIONS OF QBD

QbD is applied on an oversized scale within the pharmaceutical trade. A number of the applications are as follows;

Table 2: Benefits for regulatory agencies

S. No	Benefits for regulatory agencies	
1.	Better coordination	QbD facilitates improved coordination across review, compliance, and inspection functions within regulatory agencies, leading to a more streamlined, and effective oversight process.
2.	Enhanced regulatory submissions	QbD results in higher-quality and more informative regulatory submissions, which aid in the review and approval process.
3.	Consistency	It promotes better consistency in regulatory decisions, ensuring that evaluations and approvals align with established scientific principles.
4.	Improved review quality	QbD encourages the establishment of a quality management system for chemistry, manufacturing, and controls, which enhances the overall quality of product reviews.
5.	Flexibility in decision	Making: Regulatory agencies gain more flexibility in decision-making processes, allowing for adjustments based on scientific understanding.
6.	Science-based decisions	Decisions are rooted in scientific knowledge rather than empirical data, ensuring that regulatory actions are well informed.
7.	Interdisciplinary decision-making	QbD involves various disciplines in the decision-making process, fostering a more holistic, and comprehensive approach.
8.	Resource allocation	Regulatory resources can be directed toward addressing higher-risk areas, increasing overall effectiveness.

QbD: Quality by design

Table 3: Benefits for pharmaceutical industry

S. No	Benefits for pharmaceutical industry	
1.	Improved product design	QbD ensures better product design, resulting in fewer manufacturing problems and a higher level of product quality.
2.	Reduced supplements	Fewer post-market manufacturing supplements are required because QbD relies on understanding and mitigating risks during the design phase.
3.	Innovation-friendly	QbD allows the industry to implement new technologies for manufacturing without facing excessive regulatory scrutiny.
4.	Cost reduction	The implementation of QbD can lead to a possible reduction in overall manufacturing costs, as it aims to minimize waste and inefficiencies.
5.	Efficient regulatory process	Pharmaceutical companies experience less hassle during the review process, resulting in reduced deficiencies and quicker approvals.
6.	Enhanced interaction with regulatory agencies	Interactions with regulatory agencies occur on a science-based level, promoting a more collaborative and productive relationship.
7.	Continuous improvement	QbD supports ongoing improvements in both products and manufacturing processes, ensuring that the industry stays at the forefront of quality and innovation.

1. Using pharmaceutical QbD to increase the solubility and dissolve sophistication II BCS surfactants, crystallization inhibitors, drugs, and exploitation chemical compounds of tablets with controlled release.
2. Using QBD to create analytical separation methods: As analytical separation strategies are utilized for internal control analysis of API and medicinal products, it was concluded that the application of QbD to these strategies was necessary. HPLC and capillary electrophoresis methods were employed in the inquiry.
3. A QbD approach on starch-based nanocapsules: A potential delivery system for topical drugs. The study's goal was to create a new topical nanoparticle carrier system based on starch. Delivery of bioactive lipotropic compounds. Emulsification-solvent evaporation was the procedure that was previously utilized.[21]
4. Analytical technology using near-infrared and Raman spectroscopy silicone-based drug reservoirs are produced using the following tools: As a part of the QbD framework, the FDA's method analytical technology (PAT) focuses on "enhancing pharmaceutical development, producing, and quality assurance through innovation in product and method analysis, method control, and method development".[22]
5. Weiyong Li outlines a three-step technique development/optimization plan for HPLC assay/impurity strategies for prescription medications, namely multiple-column/mobile part screening, extra separation optimization using several organic modifiers on the mobile portion, and multiple-factor approach optimization using Plackett–Burman experimental designs are all examples of separation optimization techniques.[23]
6. Associative HPLC technology development for drug products/substances: Gradient time, temperature, the pH of the aqueous effluent, and stationary part are four often essential HPLC parameters. Square measure was assessed using a columnar data set and PC modeling code in accordance with the standards of the search framework.[24]
7. Pharmaceuticals: Pharmaceutical items are expected to deliver medications with the appropriate purity, potency, and delivery rate. Although pharmaceutical laws have unquestionably safeguarded the guys from any undesirable injuries that happened early in the 20th century.
8. In-gel manufacturing: QbD approach to a pharmaceutical gel manufacturing method, using near-infrared observation of composition and physical parameters gel NIRS method combined with multivariate geometric tools.
9. Protein synthesis and characterization: To create and characterize a new antibody manufacturing process, a scientific quality on purpose (QbD) strategy was used.[25]
10. In nanomedicine, QbD on the rational creation of a stable liquid formulation of nanomedicine products.
11. Biopharmaceuticals: QbD has also been used in biopharmaceuticals. It is a rapidly expanding industry, similar to pharmaceuticals. Regulating bodies have high expectations among the explanations for the industry adoption of QbD.

Developing biopharmaceuticals entails a number of sophisticated procedures. Chromatography is also the most important unit operation in the downstream process of biomolecules, and it is frequently the initial step in purification.

Then QbD may be applied to biopharmaceutical goods. Recently, QbD has been used successfully to determine the design space for the HPLC approach for analyzing water-soluble vitamins. TPPs of high quality, CQAs, and other key factors as seen in the table, parameters were defined as square measurements. The response surface approach was desired to value the findings of the CPPs on the CQAs of the eventual product. The percentage of alcohol was the most problematic moving strength and Young's modulus. A design space can be constructed based on the results.[26]

12. Setting up system exploitation principles of QbD: An integrated set of risk evaluations and its related components produced by Roche/Genentech was designed to give an outline of product and method data for the construction of a recombinant antibody. This chapter discusses the conditions and tools needed to define acceptance criteria, an attribute testing strategy

(ATS) for product variations, and a technique for dealing with contaminants. The proper ranges for the CQAs square measure set supported their possible effects on effectiveness and safety/immunogenicity. This strategy focuses on the management of patient effects, instead of just maintaining a homogeneous analytical profile. The ATS tools were created to identify quality characteristics that required method and/or testing management or that could be captured in a very easy system to change.[27]

QbD was used in the creation of drug substances (ICH Q11), drug products (ICH Q8 R2), and analytical methodologies. The office strongly advises introducing QbD components into ANDA. Submissions received since January 2013. It will also apply to biopharmaceutical goods. The US office has already released two case studies on QbD deployment – QBD for ANDAs: An immediate-release case study tablets in April of 2012 and ANDA quality by choice: An example for change unleashed tablets Gregorian calendar month 2011.[28]

CONCLUSION

QbD technique aids in characterizing and justifying TPPs, product, method comprehension, and continual improvement. Applying the QbD principle in development ensures quality. Medications to patients, manufacturing improvements to manufacturers with significantly lower batch failures, and drug regulatory authorities can have greater trust in the product's high quality. QbD has become more important in pharmaceutical processes such as drug development, formulations, analytical techniques, and biopharmaceuticals. The most important reason for the adoption of QbD is regulatory requirements. QbD has emerged as a viable scientific method for quality assurance in the pharmaceutical industry. The pharmaceutical sector needs regulatory compliance to get its product licensed for promotion. This new QbD process presents the potential for increased regulatory flexibility moving forward. Instead of registering the method itself, the method performance criteria could be registered, and the specific method used could be considered an example of how to achieve these performance criteria. Any modifications to this method would be addressed through internal change control procedures, allowing for adaptability and continuous improvement without the need for constant regulatory revaluation. This approach streamlines the regulatory process and encourages a focus on the quality and performance of methods rather than rigid adherence to specific methodologies.[29]

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