A COMPREHENSIVE REVIEW ON THE EMERGING CONCEPT: QBD APPROACH TO ANALYTICAL METHOD DEVELOPMENT AND VALIDATION WITH REGULATORY IMPORTANCE

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Abstract:
The administration of the pharmaceutical sector is carefully regulated by a quality policy. Regulatory organizations like the USFDA propose the scientific pharmaceutical development process known as Quality by Design (QbD). Due to the increase in the number of quality issues with pharmaceutical items, it has recently become more important. QbD can be used to create quick and reliable analytical methods for critical analysis. A scientific and risk-management strategy is used to achieve method and product understanding in the QbD approach to product and method development, which begins with predetermined targets. Regulatory bodies receive additional assurance from QbD-based product development. The analytical techniques that are used to analyze pharmaceutical drug items are equally vital, and any problems with the analytical technique's design could put patients at risk for poor quality care. As of now, none of the regulatory bodies have any explicit requirements for AQbD (Analytical Quality by Design) in analytical development. Despite the fact that there isn't a formal regulatory agency directive on AQbD, a lot of effort has recently been done in this area. The goal of AQbD is to attain measurement quality. Recently, other regulatory agencies, particularly the EMA (European Medicines Agency) and other ICH countries authorities throughout the world, have shown appreciation for the idea. They are widely acknowledged by the industry as AQbD (Analytical Quality by Design) concepts. The major goal of this review is to clarify the many phases involved in creating an analytical method using a QbD approach, as well as the application of QbD to the validation of analytical procedures and the regulatory significance of applying AQbD.

Key Words: Analytical Quality by Design, Quality by Design, Analytical Target Profile, Target Product Profile

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1.0: Introduction

The quality of pharmaceuticals significantly influences the general public's health, and hence pharmaceutical production is one of the major industries that is strictly regulated and governed by competent regulatory agencies. Consequently, it is necessary to regulate the quality of medications. The pharmaceutical industry's goal is to create products and production processes that consistently produce goods that meet the requested specifications.[1] All regulatory agencies for pharmaceutical items have prioritized quality. Customer satisfaction with regard to the process, product, and service is a sign of quality. Numerous of these quality-related initiatives reflect the necessity for businesses to succeed in the global marketplace.[2] Recent warning letters and recalls have increased speculation about the quality of pharmaceutical items and led to increased regulatory monitoring. The ICH has released several guidelines (Q8, Q9, Q10, Q11, and Q12) regarding the use of process analytical technology (PAT) tools and QbD.[2-4]

Pharmaceutical QBD is a methodical, scientific, risk-based, all-encompassing, and proactive method of developing pharmaceuticals that start with pre-established goals and emphasizes product and process control and knowledge. Quality should be incorporated by design, according to the ICH Q8 guidelines, which stipulates that "quality cannot be tested into products." ICH Q8 defines QBD as a methodical approach to development that starts with predetermined goals and places importance on product and process knowledge and control activities, based on relevant science and high-quality risk management.[5] Designing and creating formulas and manufacturing procedures that guarantee the fulfillment of predetermined product standards is known as "quality by design." The FDA unveiled a new project in 2002. (A Risk-based Approach: cGMP for the 21st Century). This program aimed to create a new regulatory framework centered on the QBD quality system and risk management, as well as modernize the FDA's oversight of pharmaceutical quality. The effort pushed the market to seek ahead quality by testing (QBT) to guarantee product performance and quality. Understanding how process and formulation factors affect product qualities is a key component of QBD, and it is crucial to identify ways to optimize this area to track them online during the manufacturing process.[6]

Regulatory organizations expect QbD to improve product and process understanding, lowering patient uncertainties. It provides a clearer understanding of the process and lessens the regulatory load from the manufacturer's viewpoint. It allows regulators more regulatory freedom without compromising product quality, and it increases patient confidence in the product's quality. Thus, the deployment of QbD benefits producers, regulatory bodies, and patients alike.[7]

One of the crucial elements of pharmaceutical research is analytical testing. In addition to guaranteeing that a drug's quality is reached by its intended therapeutic use, a reliable analytical method also provides a purity check in every stage of the product development life cycle. Since the decision to release a product into the market is based on the last quality control reports of the finished product along with other batch parameters, the analytical method used for commercial product manufacture must be time-saving, reliable, and accurate. Estimating the physical, physicochemical, chemical, and/or biological parameters of the target substance is a common component of analytical procedures. Utilizing chromatographic analytical techniques like Gas chromatography (GC), High-performance liquid chromatography (HPLC), supercritical fluid chromatography (SFC), and High-performance thin layer chromatography (HPTLC), is very common because of their many compared to non-chromatographic methods. They need fewer samples and are sturdy and adaptable. These methods reduce the possibility of human error by using automation. The development of an analytical procedure that precisely serves the intended function is the analytical chemist's top priority. There are currently two methods used for developing analytical methods in analytical chemistry.

Trial and error is the foundation of the conventional methodology for developing analytical methods. Using his past information, the analytical chemist optimizes each factor individually in this method. While using this method may produce steady method conditions, they might not be the best ones. The resilience of the approaches created using a conventional methodology could be a problem. Quality by design is a different strategy for the creation of analytical methods. Starting with identifying the separation goals, executing the risk assessment, carrying out the experiment design, and defining the control plan and MODR, it is founded on solid scientific information. There are numerous techniques described that were developed based on the QbD concept, but there are no precise criteria for the development of QbD-based analytical methods.[8-23] The current review paper provides a much more concise summary of the fundamentals

of AQbD, as well as its many components, regulatory viewpoint on AQbD, and use of AQbD in the creation of analytical methods for a generic product.

2.1:Analytical Quality by Design (ABQD)

Defining the target method profile and separation goals is the first step in the organized approach to designing the methods known as "Analytical Quality by Design" (AQbD) **(Figure-1).** The main areas of attention in AQbD are the comprehension of method controls and parameters, based on high-quality risk management and reliable science. Along with other elements like process parameters, equipment operating conditions, material attributes, completed product standards, and in-process controls, AQbD is a crucial component of control strategy in product development. Although regulatory bodies do not outline a precise AQbD method, a parallel strategy can be developed based on product QbD. For example, CQA (Critical quality attributes) can be understood as a tailing factor, the resolution between neighboring peaks, plate count, etc. in the Quality Target Product Profile (QTTP) and Quality Target Method Profile (QTMP), respectively. Method operable design range (MODR) is another name for design space.[24-25] Critical method parameters (CMP) in AQbD are determined by the methodology used and the method's intended use. To narrow down the CMPs, risk assessment is carried out based on past knowledge. The CMPs are optimized using the Design of Experiment (DoE) method. DoE aids in comprehending how input factors interact and how those interactions affect certain replies**.** To achieve regulatory flexibility and to lessen Out of specification (OOS) and Out of trend (OOT) outcomes, it is desired and advised to use the AQbD paradigm when developing analytical methods.[7] The following are the actions that must be taken to construct an analytical method using QbD principles: Project commencement, literature review, initial risk assessment, identification of ATP, creation of a method with DOE, Control Strategy and Risk Assessment, MODR, validation of the AQbD method, and ongoing method monitoring.

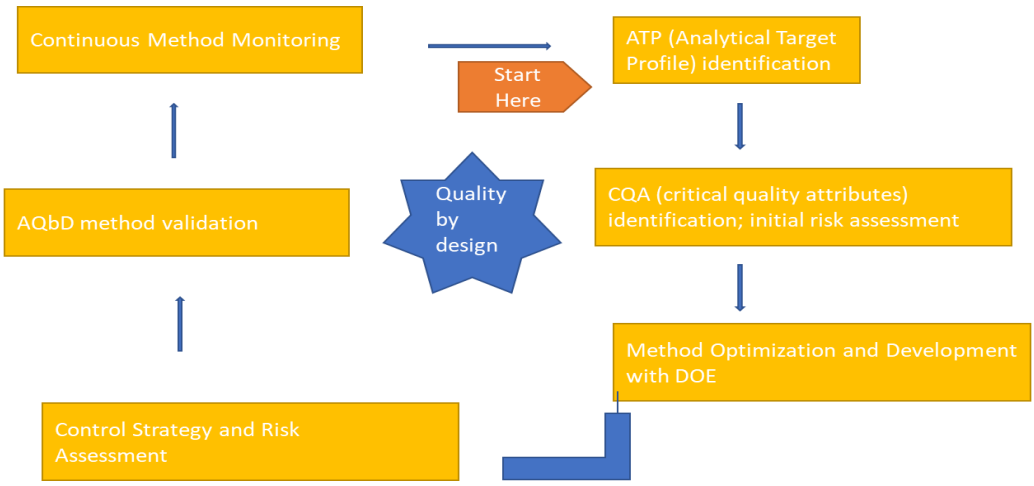

Figure 1: AQbD tools and life cycle

3.0: AQbD Development Process

3.1: ATP (Analytical Target Profile)

Since QbD is a methodical approach to developing software, processes, and products, it begins with identifying the method's aim or purpose. In this time when understanding of products and processes is under pressure, ATP is a means for developing new methodologies. It outlines the strategy requirements for the systems that will be assessed. ATP establishes the analytical variables to be evaluated (such as a specific amount of contaminants) and the performance parameters to be acquired by these assessments by using material, product qualities, and process as inputs (e.g. accuracy, distance, and precision). ATP illustrates the connection between the formulation or chemical procedure and the final analytical method. The requirement for a particular analytical technique to assess impurities at a specified level can be described in ATP, for instance, just as a chemical process is defined. Then, different strategies can be created to fulfil ATP across the development cycle; for instance, a general strategy could be employed to fulfil ATP early on in the development cycle. At the time of the product launch, a more effective technique could be created that meets the initial ATP. The ATP's strategy is primarily motivated by the need for more assay

method flexibility and by the goal to prevent expensive post-approval modifications to recorded analytical methods that necessitate early conversations with regulatory bodies. However, since just ATP will be registered in this case, each ATP-relevant method will be fully validated and documented without requiring changes to the registered methods.[26]

The whole life cycle of an analytical technique must be used to demonstrate its suitability for the intended purpose. To accomplish this, a three-stage QbD approach for pharmaceutical analysis has been developed, consisting of Procedure Design and Development, Advanced Procedure Performance Verification, and Procedure Performance Qualification by process validation in the desired manufacturer.[27] Selecting method requirements, such as target analytes (products and contaminants), product specification, and analytical technique category is part of the identification of ATP. To predict method needs and analytical criticality, a preliminary risk assessment will be made. The following are examples of ATP used in analytical procedures:

Target analytes (API and impurities) should be chosen first, followed by techniques (GC, HPLC, HPTLC, Chiral HPLC, Ion Chromatography, etc.), and then requirements for the method (test profile, solvent residue impurities).[27]

3.2: CQA (Critical Quality Attributes)

CQA is a chemical, physical, microbiological, or biological property or characteristic that needs to fall within the right range, limit, or distribution to guarantee the intended product quality, according to ICH Q8. Method properties and method parameters are included in the CQA for analytical methods. CQA can vary depending on the analytical method used.

✓ For HPLC (RID or UV), mobile phase buffers, pH of mobile phase, column selection, diluent, organic modifier, and elution method are CQA

✓ For the GC technique, the CQA includes injection temperature, the oven temperature and its program, gas flow rate, sample concentration, and diluent.

✓ The CQA for HPTLC includes, the TLC plate, injection concentration and volume, mobile phase, color development reagent, plate development time, and detection methods.

CQA for the creation of analytical methods can also be described by chemical and physical characteristics of the drug component and impurities, such as charged functional groups, polarity, solubility, boiling point, pH value, and solution stability. Before studying any potential effects on method development, the factors that affect the product's safety and quality are first sorted out. Sorting out the CQA will be made easier with knowledge of the product and process. It is thought to be a crucial quality aspect for the medicinal molecule HPLC method development if the drug product has an impurity that could directly affect its quality and safety By proving quantifiable control over quality qualities, such as the product, it is possible to achieve intermediate specification, safety and specification, and process control efficacy.[1]

3.3: Initial Risk Assessment

Risk assessment is a method for identifying the material characteristics and procedure parameters that is based on science which is employed in quality risk management (ATP). From the early stages of method development to ongoing method monitoring, risk assessment can be done. The AQbD strategy entails the identification of risks at the earliest phases of development, followed by proper mitigation measures and established management strategies. Ishikawa fishbone diagrams can be used to identify and evaluate risks in general. See

Figure- 2 for an example analytical test procedure using the fishbone risk detection approach.[28,29]

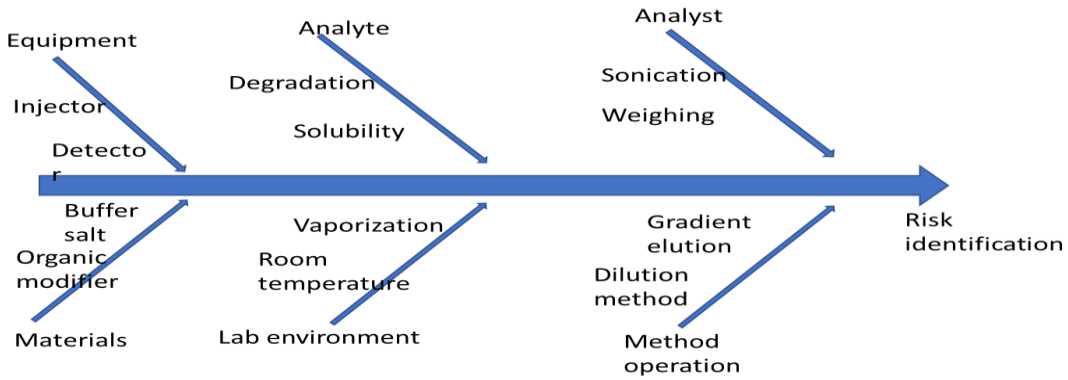

Figure 2: Fishbone for Risk identification.

3.4: Design of Experiments (Method Optimization and Development)

Design of experiments (DOE) is a method for gaining a better insight into the relationships between variables that affect a process's outputs. When DOE is used in the production of pharmaceuticals, the inputs are the characteristics of the raw materials (eg. particle size) and the process parameters (eg. Time and speed), and the output data are the crucial quality characteristics, such as tablet hardness, blend uniformity, thickness, and friability. It is hard to experimentally study all the output, input, and process parameters that are present in each unit operation. Scientists must apply risk management and prior knowledge to pinpoint the crucial input, output, and process factors that DOE needs to research. Results from DOE can be used to pinpoint ideal conditions, the crucial variables that have the biggest effects on CQAs, and those that have little to no impact, as well as specifics like the presence of synergies and interactions between variables. The permissible range of CQAs can be used to establish the design space of CPPs. To confirm that the model created at the small size is predictive at the large scale, however, scale-up may require further experimental study. This is because due of the fact that while certain crucial process parameters depend on size, others do not. Because of scale-up, crucial process parameters' operating ranges will need to shift. Due to the common usage of the same technology and excipients by pharmaceutical companies, prior knowledge can be quite important in this situation. Pharmaceutical scientists can frequently specify important material qualities, operating ranges, and processing parameters, by drawing on prior experience.[30]

3.5: MODR (Method Operable Design Region)

The MODR is the design space within which the analytical technique is anticipated to satisfy the specified Quality target method profile known as the operational design range (QTMP). It aids in the identification of key method elements and their ideal operating ranges, from which a stable area for key method parameters might be derived. For the approach to be resilient, MODR should always be greater than Normal operating limits (NOR).[7]

3.6: Control Strategy

Control techniques are established based on the method sensitivities and Method Operable design range discovered during DoE research. The control approach can take the form of determining the system's suitability, establishing the quality of reagents used for analysis, or outlining any other special safety measures to be taken while conducting the study. Below are a few instances of the control approach.

- ✓ If the DoE indicates that the distance between two adjacent peaks is crucial, resolution parameters between two peaks should be included in the determination of the system's eligibility for routine analysis.
- ✓ Similarly, the best brand and grade of reagent should be indicated in the standard testing process if the chemical or reagent utilized for analysis is crucial for chromatographic separation.
- ✓ A sonicator is used to remove the drug from the sample matrix during sample preparation. The temperature during sonication may be the most important technique parameter since few medicines are sensitive to heat stress. Therefore, the normal test process must include a precaution related to temperature management during sonication.

The control strategy is finalized using all the knowledge that was acquired during the various QbD processes, such as experiment design, risk assessment, and method operable design range. It aids in implementing essential checks and balances into the analytical process to prevent analysis failures.[7]

3.7: Validation of AQbD Method

Analytical methods are validated on various API batches using the AQbD method validation approach. This method designs method validation for any type of API build updates without re-validation using DoE and MODR expertise. This method offers all the components required for ICH validation as well as details on interactions, control tactics, measurement uncertainty, and continual improvement. Compared to conventional validation methods, our methodology uses fewer resources without sacrificing quality.[31] As a result, AQbD integration into the production process can be utilized as a control technique to guarantee the functionality and quality of the intended product. As well as facilities, completed product standards, instrument operating settings, related techniques, and frequency ranges, this also covers metrics and attributes connected to medical medicines and ingredients.[32]

3.8: Continuous Monitoring Method (CMM)

A control approach used to execute the design space in the commercial phase is life cycle management. The CMM represents the last phase of the AQbD life cycle. The method of sharing

knowledge developed throughout the formation and maintenance of the design space is known as AQbD. It also bridges the design space, control strategy, MODR, ATP, and CQA. This covers the outcomes of the risk assessment, assertions of previous knowledge, statistical design requirements, and the spanning between the ATP and design space. The method can be used for regular tasks after method validation is finished, and its continuous performance can be checked. Control charts, method-related investigations, tracking system compliance data, etc. can all be used to execute AQbD. Analysts may proactively identify and resolve out-of-trend behavior thanks to CMM.[31,33]

4.0: Differences between the Conventional Approach and QbD

A rigorous approach to method development, QbD is underpinned by in-depth scientific understanding. By design, it aids in strengthening the analytical method's resilience. Critical quality criteria and method intent are specified in detail. Each analytical procedure parameter is selected based on current scientific knowledge. The critical method parameters are identified by risk assessment, and they are then optimized utilizing the design of experiments (DoE). Ranges for method operable design are created using DoE. The identification of method sensitivities that are controlled by control strategy is also aided by AQbD.

The "trial and error" strategy is typically used to develop procedures in the conventional approach. The typical approach to method development does not thoroughly examine every aspect, therefore it's possible that certain important details (such as method sensitivities) could be overlooked. As a result, it is impossible to implement effective controls to prevent failures. In comparison to the QbD technique, more experiments are required to obtain the desired conditions. The finalized circumstances may be stable but not ideal if the standard approach was used.[7]

5.0: Problems in the adoption of QbD[1]

- ✓ Internal resistance inside the company
- ✓ A lack of available technologies.
- ✓ Not having faith in a business case. Presumably, the implementation of QbD for drug substance synthesis would necessitate more clinical trials or longer filing times for generic pharmaceuticals.
- ✓ Different FDA offices treat QbD differently. It is thought that the FDA might not consistently review filings.
- ✓ The international regulatory agencies are not aligned.
- ✓ Cooperation with outside parties. A complex supply chain including both suppliers and contract manufacturers is challenging to manage.
- ✓ Regulators are not equipped to handle applications for QbD.
- ✓ A lack of specific advice for business. Companies requested clarification from FDA on issues such as approved procedures, standards by which to determine the sufficiency of controls, criteria for analytical method replacement, and criteria to choose important quality features.
- ✓ The presented regulatory implications do not encourage QbD adoption.

6.0: Application of QbD in analytical methods of measurement[1]

QbD refers to the proper analysis carried out at the appropriate time and is based on risk assessment and science rather than necessarily implying less analytical examination. Pharmaceutical firms are using this QbD concept since it helps to develop tough and reliable methods that aid to comply with ICH guidelines. This strategy makes method improvement possible over time. Although not all pharmaceutical industries have implemented it, it may do so in the future since regulatory agencies may make it mandatory. The multiple advantages of this approach and its simplicity in complying with regulatory authorities make it possible for industries to embrace it voluntarily. The European Federation of Pharmaceutical Industries and Association (EFPIA), the Analytical Technical Group (ATG), and the Pharmaceutical Research and Manufacturers of America (PhRMA) have all provided clear ideas about how to use QbD alongside analytical methods. QbD can be used with a variety of analytical techniques, such as

- ✓ Chromatographic methods such as HPLC (For method development, stability studies, and identification of impurities in pharmaceuticals).
- ✓ Advanced methods including capillary electrophoresis, UHPLC, and mass spectrometry.
- ✓ LC-MS, a hyphenated method
- ✓ Biopharmaceutical procedures
- ✓ Vibrational spectroscopy, such as the UV technique, is used to identify and quantify chemicals.
- ✓ Studies on dissolution
- ✓ Moisture content determination using the Karl Fischer titration.

- ✓ Investigation of genotoxic impurities.

7.0: Regulatory aspects to QbD

QbD is a systematic development method that starts with established objectives and stresses process and product knowledge and control activities, based on strong science and quality risk management, according to ICH Q8 (R), Step 2. The main demand from regulatory bodies is to provide high-quality products utilizing production methods that reliably fulfill the products' intended functions. Aspects of drug ingredients, container closure systems, excipients, and manufacturing procedures that are crucial to product quality should always be identified, and control measures should be created, according to the regulatory agency's expectations. Through an evaluation of the degree to which their alteration can affect the quality of the drug product, vital formulation features and process conditions should be recognized. Scientific understanding should be provided to support the creation of the design space, manufacturing controls, and specifications by the information and expertise gathered during manufacturing experience and pharmaceutical development studies. The foundation for effective risk management should be data from pharmaceutical development research. It is crucial to understand that products cannot be assessed for quality; rather, quality should be incorporated into the design from the beginning. Changes in formulation procedures and manufacturing during development and lifecycle management should be viewed as chances to learn more and advance the development of the design space.[4]

Similarly, to this, it can be beneficial to include pertinent information learned from experiments that produced unexpected results. The regulatory agency evaluates the design space that the applicant has suggested, and after the design space has been approved, changing anything within it is not seen as a change. The fundamental idea of QbD can be generalized to the creation of analytical methods even though ICH Q8(R) does not specifically address QbD application in analytical methods. In addition to formulation QbD, the important components of AQbD are defining the analytical method profile, identifying the important method parameters, creating the design space, and implementing the appropriate control approach. The QbD-related approach to analytical methodologies has been used in certain NDA submissions that the FDA has also accepted. For moves inside the "Design Space" analytical procedure, regulatory latitude has been provided.

The main areas of attention in AQbD are the comprehension of method controls and parameters, based on reliable science and high-quality risk management. Along with other elements like process parameters, equipment operating conditions, material attributes, in-process controls, and completed product standards, AQbD is a crucial component of the product development control strategy. Although regulatory bodies do not outline a precise AQbD method, a parallel strategy can be developed based on product QbD, for example. Critical quality attributes (CQA) can be understood as tailing factors, plate count, resolution between neighbouring peaks, etc. in the Quality Target Product Profile (QTTP) and Quality Target Method Profile (QTMP), respectively. MODR is another name for design space.[34,35] Critical method parameters (CMP) in AQbD are determined by the methodology used and the method's intended use. To narrow down the CMPs, risk assessment is carried out based on past knowledge. The CMPs are optimized using the Design of Experiment (DoE) method. DoE aids in comprehending how input factors interact and how those interactions affect certain replies. To achieve regulatory flexibility and to lessen Out of trend (OOT) and Out of specification (OOS) outcomes, it is desired and advised to use the AQbD paradigm while developing analytical methods.

7.1: Regulatory challenges and inspection

The regulatory burden is reduced under a QbD model since there are greater ranges and constraints based on process and product knowledge. Changes that fall within these parameters don't require prior approval. Inspections have historically been conducted in collaboration with the FDA system-based approach and CDER's Compliance Program. The issue of how the inspection will be conducted, however, emerges in the current environment where QbD is required. During pre-approval or pre-license inspections by the QbD definition, the inspection of the FDA will assess the implementation and efficacy of the process design as specified in the application, besides whether knowledge and risk management have been effectively moved from production to manufacturing. The inspection will evaluate the effectiveness of the quality system in terms of consistent product quality, process changes, change in control processes, deviation management, risk management, and information throughout the lifecycle of the product. Raw material screening, supplier management, and equipment qualification, and facility and servicing

will all be done as before. Programs that demonstrate correctness and robustness in design, testing, and monitoring, however, will be highlighted.[8]

7.2: Benefits of Implementing QbD for FDA[36]

- ✓ Improves the review's scientific foundation
- ✓ Allows for additional decision-making latitude
- ✓ Ensures greater consistency
- ✓ Greater coordination between review, compliance, and inspection is made available.
- ✓ Information in regulatory submissions is improved
- ✓ Enhances the standard of reviews
- ✓ Use resources to deal with greater dangers
- ✓ Involves numerous disciplines in decision-making and ensures that conclusions are based on science rather than empirical information.

7.3: Benefits to the Industry[36,37]

- ✓ Relies on process and risk analysis and risk mitigation to reduce the number of manufacturing supplements needed for post-market adjustments
- ✓ Ensures better product design with fewer production issues and the potential to reduce manufacturing costs overall
- ✓ Ensures less review effort, decreased flaws, and quicker approvals
- ✓ Enables the use of new technologies to enhance manufacturing without facing regulatory scrutiny and permits ongoing improvements to both products and the manufacturing process
- ✓ Enhances interactions with FDA by dealing at the scientific level rather than the process level

8.0: Conclusion

A unique approach to pharmaceutical quality, quality by design, must be a part of the contemporary trustworthy notion. Applying the QbD concept to analytical procedures is appropriate because the outcomes of the method depend significantly on several variables, including the calibration model chosen, sample characteristics, instrument settings, and process parameters. The development and validation of analytical procedures through QbD are essential for ensuring the quality of the finished product in the pharmaceutical industry. The outcome of AQbD is understanding from product creation through commercial production. Conclusion: Understanding processes and giving opportunities for risk assessment and the development of control methods during process design and development are significant benefits of the Quality by Design (QbD) approach. The approach's overall advantages include improved method proficiency, reduced variability, and fewer trials, which lead to lower method costs and quicker method execution, as well as an understanding of the method's extreme restriction, which when crossed may lead to method failures and occasionally method alternatives.

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