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Review

Review on analytical quality by design method of improved stability of drug

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Abstract:
The stability of pharmaceutical drugs is a critical factor affecting their efficacy, safety, and shelf-life. Traditional stability testing methods often lack efficiency and may not adequately predict real-world performance. Analytical Quality by Design (A QbD) has emerged as a systematic approach to ensure product quality by designing and controlling analytical procedures. This review explores the application of QbD methodologies in improving the stability of pharmaceutical drugs. The review begins with an overview of the principles of A QbD and its significance in pharmaceutical development. It then delves into the challenges associated with drug stability testing and the limitations of conventional approaches. Next, the application of A QbD principles in designing stability-indicating analytical methods is discussed, focusing on critical quality attributes (CQAs), risk assessment, and method development strategies. Finally, future directions and challenges in the application of A QbD for improving drug stability are discussed. Areas for further research and development, such as the integration of advanced analytical techniques and computational modelling, are identified to enhance the effectiveness of A QbD approaches in ensuring drug stability and quality.

***Keywords**: quality by design, analytical, QbD, A QbD*

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INTRODUCTION

Quality should be built in by design, it cannot be tested in a product, is the main precept of 'Total Quality Management'. To attain this goal of reform quality Product, the understanding information from pharmaceutical development studies and manufacturing Provide the scientific background. Quality by Design (QbD) ICH guidance Q8 (R2). **Describes QbD as, "a systematic approach to Pharmaceutical development that begins with predefined Objectives and emphasizes product and process Understanding and process control, based on sound Science and quality risk management".[**1] As the idea moves toward a "desired State" with "regulatory flexibility," it emphasizes the development of scientific knowledge, superior design, performance demonstration, quality risk assessment (QRM), experiment design (DoE), process analytical technology (PAT) tools, ongoing learning and improvement, and life cycle management. The distinction between QbD and the current technique depends on the information learned during process understanding.[2]

International Conference on Harmonization (ICH) document Q8 (R2) describes the suggested contents for the (pharmaceutical development) section of a regulatory sub-mission in the ICH M4 Common Technical Document (CTD) format. To provide reviewers and inspectors with a comprehensive understanding of the product and manufacturing process is the aim of the Pharmaceutical Development department.[13] The document underscores one of the basic tenets of QbD that quality cannot be tested into the products, (i.e., quality should be built in by design). The information and knowledge gained from pharmaceutical development studies and manufacturing experience

provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls. Working within the design space is not considered a change, while movement outside the design space is considered a change that would normally initiate a regulatory post approval change process. When the design space is expanded with enhanced knowledge of product performance over a wider range of material attributes, processing options, and process parameters, opportunities exist for more flexible regulatory approaches, (e.g., risk-based regulatory decisions, manufacturing process improvements within the approved design space without further regulatory review and reduction of post approval supplements. As such, both industry and regulators have recognized the benefits of adopting a QbD approach to drug development and manufacture. [14] Although QbD concepts have not been codified for analytical development, the analytical community finds concepts like quality included by design but not tested into the product—a developed analytical method with meaningful system suitability criteria that aid in identifying failure modes—and working within a design space—that is, knowing the parameters of a method that affects its performance without needing to seek regulatory approval of the modified method—to be very appealing.[10] There are many definitions of quality, and most of them are vague. The FDA defines pharmaceutical quality as ensuring that no unexpected impurities create new risks, that a robust manufacturing system is ensured, and that the medication functions clinically as indicated by the label. To ensure this, the FDA unveiled the concept of "quality by design" (QbD) early in the new millennium. [8] The awareness that greater testing does not always equate to a higher-quality product was the inspiration behind this concept. However, pharmaceutical items must combine quality. The primary subjects of this review are the many quality components by design and application in the formulation of liquid crystal nanoparticles. When QbD is applied to the formulation of LCNPs, there will be multiple benefits that flow from easier transfer from bench to bedside to more robust product understanding of the product and process, process flexibility within the design space, and the implementation of more effective and efficient control strategies.[5] Analytical sciences are considered an integral part of Pharmaceutical development. Analytical method and Product development go hand in hand during the entire Life cycle of any pharmaceutical product. The traditional Approach of analytical method development is quite Tedious owing to high degree of variability involved at each stage of method development. In order to eliminate. [2, 3]

Quality by Design (QbD) is a systematic method of drug Development that aims to ensure quality by incorporating Analytical and risk-management approaches into the design, Development and manufacture of new medications; [4]

1. Integrating quality from the outset into workflows is the primary objective of QbD. Early in a program, objectives and key qualities of a product are outlined. Data and risk analysis are then used to ascertain how procedures might impact a product's properties.[4]
2. Because of this, QbD offers a strong framework for creating and executing procedures that meet predetermined Criteria and maintain a consistent level of quality. Numerous processes can be used to create and then manufacture pharmaceutical goods. Both the International Council Harmonization (ICH) and the USFDA have given their approval. [6]
3. "Quality by Design" (QbD) is a methodology that emphasizes both the product and the process while taking a methodical approach to development. It begins with a predetermined aim [5]
4. Among the many statistical and quality tools and procedures that comprise QbD are statistical quality control, multivariate statistics, and statistical designs of experiments.[9]

HISTORY BACKGROUND

The Food and Drug Administration (FDA) published a draft of "Current Good Manufacturing Practices" (cGMP) in 2002 with regard to pharmaceutical quality. Modernizing the pharmaceutical industry for the twenty-first century was the main goal of the project. . [9, 10, 12]

Table 1: History of QbD

Year	Activities
1950	Operation windows
1970	QBD created by Joseph M Juran
2002	QBD concept integrated by USFDA in cGMP
2004	USFDA release final report in “Pharmaceutical cGMP”
2009	ICH: Q8(R2) Pharmaceutical Development
2005	ICH: Q9 Quality Risk Management
2008	ICH: Q10 Pharmaceutical Quality System

Approximately 5,000 manufacturing supplements were submitted to the FDA in 2007—a notable increase in the quantity of supplements to applications for new drug applications (NDAs), Biological License Applications (BLAs), and abbreviated new drug applications (ANDAs). FDA noticed a rise in the number of corporations submitting lapsed

NDAs or AN-DAs, and a significant number of additional applications were received for each manufacturing change. The data mostly concentrated on chemistry in both the original applications and the supplements. [13] Furthermore, other crucial production processes like engineering and product development received the least attention. In due course, the FDA came to recognize that an increasing number of controls were needed for drug manufacturing processes in order to produce effective drug products and, presumably, to make better regulatory decisions. It resulted in a more rigorous upbringing regarding rules. In order to solve this issue, the FDA modified Pharmaceutical cGMP (good manufacturing procedure) for the twenty-first century in 2002. Process analytical technology, or PAT, is a method for organizing, evaluating, and controlling production processes using scientific knowledge and factors that affect the final product's quality. In PAT, expectations were discussed. When the time came to implement QbD for a more systematic approach in 2005, the USFDA required that certain companies submit their CMC in QbD format (Patricia, 2007). Question-based review (QbR) serves as the cornerstone upon which the QbD concept is founded. [9]

ICH GUIDELINES AND QbD

FDA PRESPECTIVE

In 2005, the USFDA asked participating companies to provide Chemistry Manufacturing Control (CMC) data, which demonstrated the application of QbD in the New Drug Application. Quality by Design (QbD) means finishing every phase of the process; a goal is set before the process even starts. Two other prerequisites for QbD deployment are design space and real-time release risk assessment. Strict rules for product quality are established by international harmonization conferences in their Q8 pharmaceutical development, Q9 quality risk assessment, and Q10 pharmaceutical quality system. .[10] The FDA highlights the importance of pharmaceutical product quality by offering Process Analytical Technology (PAT), a framework for creative pharmaceutical development, production, and quality assurance. Ultimately, QbD helps to carry out Q8 and Q9. The FDA defines QbD as "a systematic approach to product and Process design and development." In 2004, the FDA gave their approval to this concept and offered a comprehensive justification in "pharmaceutical cGMP for the 21st century: a risk-Based approach." [11, 12]

Product quality and performance can be assured by Designing efficient manufacturing processes.

- Product and process specifications are based on a scientific understanding of how process factors affect Product performance.
- Risk-based regulatory approaches are for scientific Understanding and control related processes for Product quality and performance.
- Related regulatory policies and measures are modified To accommodate the real-time scientific knowledge.[13]

KEY CHARACTERSTICS OF QbD [15, 16]

- A tool for focused & efficient drug development
- A dynamic and systematic process
- Relies on the concept that Quality can be built in as a Continuum
- It is applicable to Drug Product and Drug Substance Development (chemicals/biologics)
- It is applicable to analytical methods
- Can be implemented partially or totally

APPLICATIONS OF QbD [17]

- Applications of QbD in analytical method development
- Applications of QbD for drug substance development.
- Applications of QbD for clinical trials.
- Applications of QbD for bioequivalence studies.
- Applications of QbD for pharmaceutical manufacturing.
- Applications of QbD for formulation development.

ADVANTAGES OF QbD [16]

- Patient safety and product efficacy are focused.
- Scientific understanding of pharmaceutical process and methods is done.
- It involves product design and process development.
- Science based risk assessment is carried.
- Critical quality attributes are identified and their effect on final quality of product is analysed.
- Business benefits are also driving force to adopt QbD.
- Eliminate batch failures.
- Minimize deviations and costly investigations.
- Avoid regulatory compliance problems.
- Empowerment of technical staff.

- Efficient, agile, flexible system.

STEPS INVOLVED IN QbD [15]

Development of new molecular entity

- Preclinical study
- Nonclinical study
- Clinical Study
- Scale up
- Submission for market Approval

Manufacturing

- Design Space
- Process Analytical Technology
- Real time Quality Control

Control Strategy

- Risk based decision
- Continuous Improvement
- Product performance

Application to Industry [17]

- Improves product design and reduces production issues
- Reduces the amount of manufacturing supplements required for post-market modifications; instead, it depends on risk assessment, process understanding, and risk mitigation
- Allows new technology to be used to improve manufacturing without requiring regulatory scrutiny
- Lowers waste and creates the possibility of a decrease in overall production costs.
- Ensures less hassles during the review process, fewer deficiencies, and faster approvals.
- Improves interaction with FDA –deal on a science level instead of on a process level.
- Allows for continuous improvements in products and manufacturing process

Seven steps of QbD start-up plan [15]

1. Hire an independent Quality by design expert.
2. Audit your organization and process with the expert conducting a gape analysis.
3. Hold a basic quality by design workshop with all your personal.
4. Review the expert's report and recommendation.
5. Draft an implementation plan, timelines and estimated costs.
6. Assign the resources (or contract out).
7. Retain the independent expert as your "Project Assurance" advisor.

Potential benefits of adopting QbD for analytical method [14]

1. Scientific understanding of pharmaceutical process and method.
2. It provides a space for invention of new techniques by continuous improvement throughout life cycle.
3. Critical quality attributes are identified and their effect on final quality of product is analysed.
4. It provides required design space for development.
5. Flexibility in analysis of API, impurities in dosage forms, stability samples, and metabolites in biological samples.
6. Reduction in variability in analytical attributes for improving the method robustness. 11
7. Minimize deviations and costly investigations.
8. Smooth process of method transfers to the production level.
9. It provides greater compliance with regulatory authorities.

FLOW OF QbD [15]

Define target product profile and quality target profile

↓

Identify critical quality attributes

↓

Carry out risk assessment linking material attributes and process parameter to CQAs

↓

Establish design space

↓

Describe control strategy

↓

Life cycle management and continuous improvement

Benefits of Analytical QbD [1, 2]

- Increased understanding and control
- Beyond traditional ICH procedure of method Validation
- Flexibility in analysis of API, impurities in dosage Forms, stability samples, and metabolites in Biological samples
- Reduction in variability in analytical attributes for
- Improving the method robustness
- To keep the values of analytical attributes within the Pharmacopoeia monographs, and away from Out Of Specification (OOS) limits
- Smooth process of method transfer to the production Level
- No requirement of re-validation within MODR

AQbD/QbD comprises of all elements of pharmaceutical development described in ICH Q8 depicted in above Figure.

STAGES IN QbD AND AQbD

Stage	**QbD**	**AQbD**
STAGE 1	Define Quality Target Product Profile (QTPP)	Define Analytical Target Profile (ATP)
STAGE 2	Critical Quality Attributes	Critical Quality Attributes
STAGE 3	Risk Assessment	Risk Assessment
STAGE 4	Design Space	Method Operable Design Region
STAGE 5	Control Strategy	Control Strategy
STAGE 6	Life Cycle Management	Life Cycle Management

Table 2: Stages in QbD &AQbD

DIFFERENCE BETWEEN QbD AND AQbD

QbD	**AQbD**
Quality is assured by testing and inspection.	Quality is built into product & process by design and based on scientific understanding.
Here, any specifications are based on batch history.	Here, any specifications based on product performance requirements.
It includes only data intensive submission which includes disjointed information without "big picture".	It includes knowledge rich submission which shows product knowledge & process understanding.
Here there is "Frozen process," which always discourages any changes further.	Here there is flexible process within design space which allows continuous improvement during the product life cycle.
It focuses on reproducibility which often avoids or ignores variation.	It focuses on robustness which understands and control variation.

Table 3: Difference Between QbD & AQbD

METHEDOLOGY

There is some methods of QbD in stability of the drug;

Method development by QbD approach [20, 21, 22]

Step 1: Defining method intent

Since pharmaceutical QbD is a methodical, scientific, holistic, threat-based, and practical approach that begins with set objectives and places a heavy emphasis on product and process awareness and control, the goals of HPLC method development must be explicitly defined. The ultimate goal of the analytical procedure needs to be the isolation and quantification of the main chemical.

Step 2: Performing experimental design

Quick and systematic procedure by using experimental design effectively, optimization can be attained. It is assumed that a systematic experimental design is necessary to achieve optimization and have a comprehensive understanding of the process. It builds a chromatographic database to aid in understanding, method selection, and method optimization. It can also be used to evaluate and carry out the method change in the event that the need arises later on—for example, if the chromatographic column that was employed is no longer available for purchase or if contaminants are no longer significant.

Step 3: Evaluation of experimental results and selection of final method conditions

The conditions of the approach must be analyzed using the three-tiered methodology. Assessing the circumstances for peak symmetry, peak fronting, and peak tailing should come first. After that, these conditions

need to be evaluated again with more stringent requirements, such as the tailing factor needing to be less than 1.5, among others.

Step 4: Performing risk assessment with robustness and ruggedness evaluation

Based on method attributes, there's a significant chance the chosen final technique will be dependable and functional for the duration of the product. The verification and finalization of the approach, as well as an evaluation of its robustness and roughness, are the primary duties of the fourth step of method development.

Method qualification

After the analytical target profile (ATP) and associated risk are taken into consideration during the design phase, the next step is method qualification, which verifies that the technique is functioning as intended. It involves equipment qualification as well as technique qualification. The three categories are method operating qualification (MPQ), method performance qualification (MPQ), and method installation qualification (MIQ).

For an instrumental qualification demonstration, the HPLC instrument is taken into consideration. When developing a chromatographic procedure on HPLC, the following qualification can be done.

i. Installation Qualification
ii. Operational Qualification
iii. Performance Qualification

User requirement specifications (URS), a part of DQ, define the design and technical specifications of an instrument. It is the users' duty to make sure that HPLC is suitable for the intended usage because it is a commercially available system. It is the user's responsibility to confirm that the installation location complies with all environmental requirements supplied by the supplier. The IQ component begins at this point. The equipment is assembled and tested at the user's location to make sure every part works as it should.

Method development (design selection):

Fundamental to design selection is the method- development phase. To develop a QbD method, the method performance criteria must be understood as well as the desired operational intent that the eventual end user would wish to see in the method.

Method operational intent:

These specifications address the aspects of the process (such analysis time, appropriate solvents, and easily accessible equipment) that need to be fulfilled in order to make it straightforward to use in routine operations. Opportunities to introduce new or improved technology may arise. These criteria can be developed by an examination of the voice of the customer (VoC) or the components of a technique deemed important for the manufacturing quality control laboratory where the commercial methods will be utilized.

Control strategy

To guarantee that the predefined procedure functions as intended and regularly produces accurate results, control of the process is required. An element that has been determined to be hazardous must be controlled. More attention is paid to the high-risk factors. Apart from system suitability, the risk assessment can help choose a specific control strategy.

Life cycle approach

The traditional method development methodology is not the same as the life cycle approach. Additional field states that it entails continuous technique performance development and that flexibility is allowed by the design space for Owing to the established design space, continuous enhancements to the analytical technique can be carried out without prior regulatory approval.

Elements of QbD to analytical method: [20, 21]

In determination of impurity:

A quality-by-design approach to the development of impurity techniques for atomoxetine hydrochloride. An ion-pairing HPLC technique was developed and related system appropriateness criteria were investigated for the analysis of atomoxetine hydrochloride. Statistically designed experiments were used to demonstrate the technique's durability and to modify the parameters for the separation of impurities and atomoxetine. The use of multiple-column/mobile phase screening, multiple-factor method optimization using Plackett–Burman experimental designs, and additional separation optimization through the use of multiple organic modifiers in the mobile phase are all part of the development and optimization strategy for HPLC assay/impurity methods for pharmaceuticals. Computer simulations were performed using a commercial chromatography optimization application called Dry Lab.

In development of HPLC method for drug products/substances:

A leading-edge approach to applying the quality by design (QbD) concepts to the development of high pressure reversed phase liquid chromatography (HPLC) procedures. The four common critical factors in HPLC—temperature,

aqueous eluent pH, stationary phase, and gradient time—are evaluated within the quality by design framework using computer modelling tools and a column database.

In screening of column used for chromatography:

Experimental design, evaluation criteria used and some of the most commonly used analytical columns from reputed column manufacturers. A systematic approach is used to evaluate seven RP-HPLC columns against predefined performance criteria. This approach is a fundamental part of a QbD method development.

In stability studies: This paper describes the development of a stability indicating HPLC method for a complex pain management medicinal product that includes the therapeutic ingredient, two preservatives, and their degradant. Quality by design (QbD) approaches are applied to the process as well. The initial method did not resolve the oxidative degradant peaks for drug degradants and preservatives, nor the peaks for drug degradants and other substances. Using a DOE-based strategy, the process was optimized using Fusion AETM software. The QbD-based method development enabled the creation of a design space and an operating space with details about all method performance aspects, constraints, and resilience inside the operating area. [21]

In UHPLC: [21]

High prediction accuracy and speedy high performance liquid chromatography were accomplished through the use of design space computer modeling. This illustrated the applicability of computer-assisted modeling with adequate precision for UHPLC applications as well as the accuracy of retention time prediction at high pressure (increased flow-rate).

Opportunities of and barriers against a QbD approach to analytical methods: [21]

Several opportunities of this QbD approach to analytical methods, including;

- Thanks to more robust and dependable techniques, there will be less money spent on analysing out-of-spec results and more assurance in the length of analytical testing cycles.
- To ensure that the methods are truly robust and resilient, the resources currently devoted to traditional technology transfer and method validation duties will be reassigned.
- The introduction of new analytical procedures using a QbD strategy will lead to a higher transfer success rate than standard technology-transfer methodologies, which range from R&D to quality control laboratories.
- Specified process will help the systematic and successful implementation of the QbD methodology and fosters a team approach.
- A true continuous learning process is established through the use of a central corporate knowledge repository that can be applied across all methods.
- Current expectations of analytical technology transfer and method validation must change because current validation guidance does not lead to methods that can always be reliably operated.
- Acceptance must be gained for registration of the method performance criteria rather than the method conditions.
- External guidance must be developed in this area; ICH guideline Q2 (R1) requires revision (or removal) and Center for Drug Evaluation and Research guidance must be created for analytical methods.
- A common language for some of the new terms is required, including analytical method design space, analytical method control strategy, and method performance criteria.
- Analysts must learn new tools and skills
- A consistent worldwide approach is required for this initiative to be effective.

QbD for various analytical methods which include, [21]

- Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals).
- Hyphenated techniques like LC-MS
- Advanced techniques like mass spectroscopy, UHPLC, and capillary electrophoresis
- Karl Fischer titration for determination of moisture content.
- Vibrational spectroscopy for identification and quantification of compounds e.g., UV method.
- Analysis of genotoxic impurity.
- Dissolution studies
- Biopharmaceutical processes

RESULT [20, 21, 22]

Quality by Design (QbD) is an approach in the pharmaceutical industry that aims to ensure the quality of drugs by integrating product and process understanding throughout the development and manufacturing processes. When applied to improve the stability of drugs, QbD can lead to:

Robust Formulation: Designing formulations with a thorough understanding of critical quality attributes (CQAs) and critical material attributes (CMAs) helps create a more stable drug product. Process Optimization: Identifying and controlling critical process parameters (CPPs) contributes to a more consistent and stable manufacturing process, reducing variability in the final product.

Risk Assessment: Through the use of a systematic risk assessment technique, QbD lowers the probability of stability-related failures by anticipating and resolving potential stability concerns throughout the development process. Real-time Monitoring: By putting continuous monitoring and control strategies into effect, it is feasible to recognize any deviations from the anticipated stability profile and make timely adjustments to preserve the quality of the product. Decreased Batch-to-Batch Variability: Quality by Design (QbD) helps achieve more consistent product quality from batch to batch by identifying and managing sources of variability.

Lifecycle Management: QbD emphasizes continuous improvement and adaptation over the product lifecycle, ensuring that stability concerns are addressed not only during development but also throughout the commercial life of the drug. In summary, the application of Quality by Design in drug development contributes to the creation of more stable formulations, robust manufacturing processes, and ongoing quality management.

CONCLUSION [20, 21, 22]

The holistic nature of Quality by Design (QbD) extends beyond stability improvement, influencing the entire drug development landscape. QbD promotes the incorporation of cutting-edge technologies and scientific understandings into formulation and manufacturing procedures by cultivating an innovative and flexible culture. This not only takes care of the immediate stability issues, but it also sets up pharmaceutical research for long-term success in a field that is always changing. QbD's systematic and data-driven approach promotes transparency, facilitates regulatory compliance, and ultimately con-tributes to the delivery of safe, effective, and stable drugs to patients, reinforcing the commitment to high-quality pharmaceutical products.

Early risk identification during development is made feasible by applying Quality by Design (QbD) to gain a deeper understanding of formulation and manufacturing processes. QbD encourages the development of strong pharmacological products by stressing a science-based and risk-managed strategy, which increases stability and lowers the possibility of unexpected changes occurring during production. All things considered, QbD increases pharmaceutical stability while also helps with regulatory compliance and the timely administration of secure and effective medications to patients.

The application of Quality by Design (QbD), which systematically integrates scientific concepts into the formulation process, improves stability in the production of pharmaceuticals. This approach facilitates the creation of robust formulations by enabling a deeper knowledge of essential elements impacting stability. Pharmaceutical businesses can increase drug stability during their lifecycle by optimizing parameters, recognizing potential hazards, and assuring consistent product quality through Quality-Based Drug Development (QbD).

Moreover, QbD makes it easier to fully understand the formulation and production processes, which makes it possible to build lasting products with improved stability profiles. By focused risk assessment and mitigation strategies, QbD minimizes the possibility of unforeseen consequences, enhancing the long-term stability of drugs. This meticulous, scientific methodology not only satisfies regulatory requirements but also maximizes medicine development efficiency and ensures.

A thorough technique is adopted, emphasizing on critical quality qualities, risk assessment, and the identification of important elements, by incorporating QbD into pharmaceutical development. This proactive strategy optimizes the production and formulation processes, lowering the likelihood of instability and ensuring consistent product quality. QbD, which fosters a culture of continuous development, encourages the application of scientific information to make well-informed decisions that promote the stability and reliability of pharmaceutical goods over the long term.

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