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Review Article

Analytical QBD Approach to Redefine the Quality of Pharmaceuticals: A Review

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ABSTRACT

As per the present scenario traditional techniques of quality by testing of finished pharmaceutical products have proved to be unsatisfactory, although focus on 'Total quality assurance can be attained only by in-process testing and analysis. The Quality by Design (QbD) idea has already been established and applied in all nations that adhere to the International Conference on Harmonization Guidelines. The proposed ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management, and Q10 for pharmaceutical quality systems offer a foundation for incorporating quality into the product. Other components are being added and integrated into the analytical method development process, including as Quality Risk Management, the Pharmaceutical Quality System, and Process Analytical Technology (PAT) guidelines. The Quality by Design (QbD) idea has already been established and applied in all nations that adhere to the International Conference on Harmonization Guidelines. The proposed ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management, and Q10 for pharmaceutical quality systems offer a foundation for incorporating quality into the product. Other components are being added and integrated into the analytical method development process, including as Quality Risk Management, the Pharmaceutical Quality System, and Process Analytical Technology (PAT) guidelines. They are widely acknowledged in the business as AQbD (Analytical Quality by Design) ideas. This paper attempts to summarize QbD achievements to date, regulatory perspectives on QbD, a comparative examination of conventional and analytical QbD techniques in method development, and issues about its fundamental application.

Keywords: Quality by Design; Design of Experiments; Analytical Quality; Critical Quality Attributes Analytical Target Profile; Process Control

INTRODUCTION

The pharmaceutical market has long been regarded as one of the most strictly regulated industries, consistently producing high-quality drug products for human consumption with the desired pharmacotherapeutic effects for the treatment of a wide range of ailments [1]. However, over the last few decades, the pharmaceutical industry has faced on going challenges in delivering high-quality drug products [2]. The primary goal of drug development is to assure safety, quality, and efficacy; however there are other issues to consider, such as drug recalls, the cost of manufacturing failure, scale up, and regulatory load. End product testing is a traditional method of guaranteeing product quality. This is why regulatory authorities are now focusing on QbD implementation to reduce process variability and improve process quality. As a result, QbD offers a systematic and modern way to assuring constant product quality across time. Quality by Design is a concept pioneered by Joseph.M.Juran in a number of books. In his book Quality by Design, Juran highlights the elements that contribute to customer pleasure and the dependability of such features. He also proposed a Juran's triology, which defined three quality pillars: planning, control, and improvement. It is the current approach to pharmaceutical quality [3] and it contains the components of management, statistics, psychology and sociology [4].

According to ICH advice Q8 (R2), QbD is "a systematic approach to pharmaceutical development that begins with established objectives and stresses product and process understanding and process control, based on strong science and quality risk management. It emphasises a fundamental

concept of QbD: quality cannot be tested into goods it must be built in by design[5]. According to Janet Woodcock (2004), "QbD means the product and process performance characteristics are scientifically created to suit specified objectives, rather than merely empirically obtained from test batch performance." QbD is all about building an appropriate process and understanding process performance for the target product performance[6]. Simultaneous QbD operations in synthetic and analytical development will result in the highest quality product while minimising risks[7] . To assure quality, the full implementation of QbD necessitates process control of essential phases[8] . Its overall purpose is to incorporate quality into pharmaceutical products in order to preserve patient safety[9] . The advancements under QbD were listed in Table 1 . Currently, no regulatory authorities have defined standards for AQbD (Analytical Quality by Design) and PAT in analytical development.

DESIGN CONCEPTS AND BASICS FOR ANALYTICAL QUALITY

The concept of QbD can be extended to the development of analytical methods, which is known as AQbD[10]. Analytical QbD is defined as a science and risk-based paradigm for analytical method development that aims to understand the predefined objectives in order to control the critical method variables that affect the critical method attributes in order to achieve enhanced method performance, high robustness, ruggedness, and flexibility for continuous improvement[11] . It can help improve certain analytical methods that are currently utilised for quality control and analysis. AQbD is a more advanced way to develop analytical techniques based on QbD concepts. The analytical development phase is essential for characterising drug substances as well as for analysing drug(s) in dosage forms, biological matrices, and stability samples. Due to the high level of criticality seen during method development, validation, and transfer, analytical methodology is, thus a crucial component of pharmaceutical development. ICH Q14 guidelines offer scientific approaches to analytical procedure development and to give principles relevant to the description of the analytical procedure development process. These new recommendations are intended to improve regulatory communication between industry and regulators in order to promote more efficient, solid scientific and risk-based approval, as well as post-approval change management of analytical methods.

The implementation of AQbD[12] is expected to strengthen the concept of "right analytics at right time," which is important in drug product development[13] . A few months ago, the FDA approved a few NDA's that supported AQbD and emphasised the importance and application of QbD in analytical method development. It activates the analytics role in the product[14] . Furthermore; there is a need of transition from traditional checklist implementation requirements to a method validation approach that should provide a high level of assurance of method reliability in order to adequately measure the drug product's critical quality attributes (CQAs)[15]. Scientific and regulatory knowledge, as well as quality control requirements, are all considered in AQbD. While most applications have focussed on using design of experiments (DOEs) and statistical screening for method parameter operational spaces in order to consider method robustness, a systematic approach has also been advocated[16]. However, much more work is needed to perfect the AQbD procedures and spread the concept to all methods, from clinical to commercial, as well as lifecycle management[1].

BASIC ANALYTICAL QUALITY BY DESIGN TERMINOLOGY

QbD- Quality by design; AQbD-Analytical quality by design; ICH-International conference on harmonisation; FDA-Food and drug association; ANDA-Abbreviated new drug application; NDA- New drug application; ATP-Analytical target profile; CQA- Critical quality attributes; CMP- Critical method parameters; CMV- Critical method variables; QTMP- Quality target method profile; QTPP-Quality target product profile; CAA- Critical analytical attributes; DoE- Design of experiments; MODR- Method Operable Design Region; QRM- Quality risk management; AQbD strives to achieve the predefined analytical

Objectives.

The overall AQbD strategy revolves around five fundamental elements:

1. Defining the analytical target profile or quality target method profile
2. Identifying critical analytical attributes, critical method variables or critical method parameters, critical process parameters
3. Selecting appropriate experimental designs for carrying out analysis based on design of experiments
4. Accurate delineation of analytical design space or method operable design region and analytical control space or normal operating region in order to outline the best analytical solution.
5. Formulation of control strategy for continual improvement

The primary goal of AQbD has been to build strong MODR or ADS within relevant system suitability requirements, as well as to provide on-going life-cycle management.

TRADITIONAL APPROACH VERSUS AQBD

Traditional validation methods are typically evaluated only once. As a result, the possibility of method failure during transfer is always present high. Furthermore, the

performance variables are not thoroughly investigated and comprehended. Figure 1 summarises the comparison of traditional and AQbD approaches, with the goal of addressing the flaws of the traditional approach based on scientific comprehension and knowledge repository[17].More than just developing more robust methods, applying AQbd Approach to analytical methods will optimise the methods of risk assessments as well as the control assignment strategies. Using the AQbD, methods will be developed in a risk-based manner, ensuring quality assurance in all of the processes. This is a superior alternative to traditional approaches[18].

PROSPECTIVE BENEFITS OF USING QBD DURING ANALYTICAL METHOD DEVELOPMENT[19]

- Understanding, reducing, and controlling the cause of variability
- To aid both verbal and implicit comprehension of the approach
- To go beyond the usual ICH technique of method validation
- To capture in - process information for timely control decisions
- To isolate the true sources of variability by removing variability caused by external factors
- To improve technique robustness by reducing variability in analytical characteristics
- To forecast real - time influence of high - risk factors on CAAS , prior to product development
- To achieve flexibility in the examination of API, contaminants in dosage forms, stability samples, and biological metabolites
- Avoiding the requirement for revalidation inside MODR by keeping analytical characteristic values within pharmacopoeial monographs and specification restrictions.
- Choosing a design with a high chance of success and safety.
- Investigate potential failure mechanisms and their impact on system functioning.
- To lay the groundwork for feasible in-house troubleshooting methods; and
- To promote technology transfer to the production level.
- Analytical quality is achieved through the development of strategic concepts and execution procedures.

ANALYTICAL QUALITY BY DESIGN STRATEGIC PRINCIPLES AND IMPLEMENTATION STEPS

The rationale for applying QbD principles to analytical techniques stems from the fact that multitude of variables tends to influence method outputs. These factors include sample properties, equipment settings, procedure parameters, and calibration model selection. The number of variables involved in chromatographic procedures, which are the most often used analytical tools in pharmaceutical quality control, is large. The analytical method development phase is quite similar to the formulation development phase. Implementing QbD allows for regulatory flexibility, but it demands a high level of resilience, product quality, and understanding of the process, product, and analytical procedure[20]. On the ground, the implementation of the AQbD exercise may be completed effectively by following the five critical phases[21] outlined below:

- **Step 1: Establishment of ATP or QTMP**

AQbD begins with an analytical target profile (ATP), which is analogous to QTPP. ATP specifies the purpose of the analytical method development process, tying the technique's outcomes to QTPP. ATP was recently defined as "a statement that describes the method's purpose and is used to drive method selection, design, and development processes." Once the regulatory authorities approve the ATP statement, ATP is an important metric in AQbD that allows for higher continual improvement of analytical methods and their selection[22]. ATP is the core of any analytical technique established using QbD principles, and it is quite similar to the quality target product profile, whereas adopting QbD for pharmaceutical goods includes the goal of analytical procedures and quality criteria to allow for predictable results about material properties. The identification of ATP provides a defined direction for technique development, validation, and transfer, as well as future flexibility; operating within a known acceptable region PAR.

- **Step 2: Determine CAAs and CMPS**

The next phase in pharmaceutical QbD is the identification of critical quality attributes. CQA refers to the chemical, physical, biological, or microbiological features or characteristics of a pharmaceutical product (in-process or finished) that must meet particular criteria in order to be considered high-quality. Identity, assay, content, uniformity, degradation, products, residual solvents, medication release or dissolution, moisture content, microbiological limits, and physical qualities such as colour, shape, size, and friability may all be considered in CQA. QTPP potential CQA is used to assist product and process development. In order to achieve CQA and QTPP, Critical Material Attributes and Critical Process Parameters must also be identified. Analytical Method Performance Characteristics are defined to satisfy the needs of ATP. AMPC is divided into two categories based on the source of error: a) systematic (bias) variability, which includes accuracy, specificity, and linearity; and b) random variability, which includes precision, limit of detection, and limit of quantification. Furthermore, range and robustness can be mentioned in the AMPC definition. It is always advised to include a joint requirement

of technique features (at the very least, accuracy and precision) in ATP. Analytical technique selection (for example, chromatographic, spectrophotometric, or microbiological assays).

According to ICH Q9, risk assessment consists of three steps: risk identification, risk analysis, and risk evaluation. Risk identification defines all of the procedure parameters based on their potential influence on the CAAs. Furthermore, "critical few" CMPs impacting CAAs and method performance are discovered. The primary strategy generally used to offer a thorough awareness of the total risks associated with distinct CMPs while altering CAAs of the analytical method is quality risk management (QRM). CMPs are significant input factors or independent variables related to instrument settings, column chemistry and dimension, sample preparation, and so on, whereas CAAs comprise the output responses or dependent variables. The cause and effect relationship on the potential CAA of analytical methods is represented below in Figure 2

- **Step 3: Design - guided technique development and analysis**

The use of DoE principles permits strong scientific knowledge of the numerous technique factors and variables that tend to effect CAAS utilising little testing to give the most information, while minimising the prevalence of (any) interactions and lowering complexities. DoE can also be used to optimise experimental conditions using many variables. Knowledge of CAAs, CMPs, their ranges, and optimal fitting of the mathematical model (s) is required for the successful execution of the DoE research.

- **Step 4: Establishment of MODR**

Nowadays, computer-aided techniques and software are employed to optimise parameters and their corresponding reactions. MODR or ADS of any analytical approach, also known as proven acceptable range. PAR is the multidimensional integration and interaction of input variables (i.e., CMPs during analysis) that has been established to offer assurance of quality.

- **Step 5: Implementation of a control plan and continual improvement**

A designed set of controls for all conceivable variations ensures that ATP requirements are satisfied throughout analytical method transfer and routine use. This is achievable by constant monitoring of CAAs or system appropriateness criteria. Control strategy is not necessarily a one-time effort, and it should be developed across all crucial stages of the method development life cycle in order to achieve continual improvement. Even after going through all of the QbD aspects for a specific analytical method, method validation, verification, and transfer are the important activities that assure the method's suitability for its intended application.

ANALYTICAL QUALITY BY DESIGN IN LIFE - CYCLE MANAGEMENT [23]

This comes after the development of an analytical method for quality control or routine testing. Once a method has been developed for normal usage, its performance should be tracked over time to ensure that it remains in compliance with the defined ATP criteria. It is represented in the pharmaceutical industry by using control charts or other tools to track system suitability data and method-related investigations. For example, by tracking system appropriateness data with control charts or other tools, conducting method-related research, and so on. Periodic fit for purpose re-verification trials can also be carried out if necessary. This continuous monitoring enables an analyst to detect, identify, and address any abnormal or out-of-trend analytical method performance. Existing methods should be re-evaluated on a regular basis to address any gaps or improvement possibilities identified in the current methodology, either by refining the methodology or by incorporating a new technology as analytical technologies develop. The analytical method's role in control strategy is critical, and it starts with raw material testing (before manufacturing) and ends with stability testing (after marketing),

QUALITY BY DESIGN FACILITATORS [24]

Quality risk management and knowledge management are two of the most important QbD enablers. They are extremely important in QbD development and implementation they are helpful in reaching product realisation, creating and retaining control, and lastly allowing for continuous improvement.

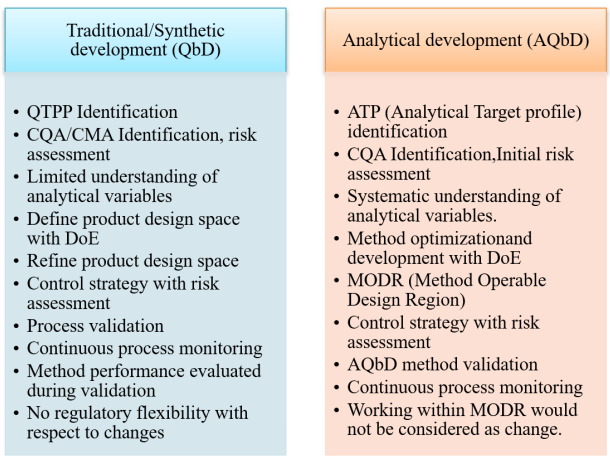

Fig. 1: Comparison of Traditional and AQBD Approaches

Table 1: Historical Background of QBD [25,26]

Year	Activities
1950	Operation windows
1970	Qbd created by Joseph M Juran
Sep 2002	Qbd concept integrated by USFDA in CGMP
Sep 2003	Pharmaceutical Cgmp for 21st century-A risk based approach second progress report and implementation plan
Sep 2004	USFDA release final report in pharmaceutical CGMP
Sep 2004	USFDA guidance for industry: PAT-A framework for innovative pharmaceutical development, manufacturing and quality control
March 2005	The European medical agency road map to 2010: Preparing the ground for future
Nov 2005	Pharmaceutical development Q8
Nov 2009	ICH: Q8(R2) Pharmaceutical development
Nov 2005	ICH: Q9 Quality risk management
June 2008	ICH: Q10 pharmaceutical quality system
Jan 2011	Guidance for industry: Process validation: General principles and practices
March 2011	EMA-FDA pilot program for parallel assessment of quality by design applications
Dec 2011	ICH-endorsed guide for ICH Q8,9,10 implementation
Feb 2012	ICH quality IWG points to consider for ICH Q8,9,10 guidelines
March 2012	Guidelines on real time release testing ,formerly guideline on parametric release
April 2012	Quality by design for ANDA's: An example for immediate release dosage forms
May 2012	Development and manufacture of drug substances
Aug 2013	EMA-FDA Pilot program for parallel assessment of QbD applications
Feb 2014	Guidelines on process validation for finished products, information and data to be provided in regulatory submissions
Sep 2017	ICH Q14: New guidelines are recommended to harmonise the scientific approaches to analytical method development based on a survey of pharmaceutical companies.
Jan 2018	The MHRA's approach and strategy for applying QbD concepts to pharmaceutical standards
Aug 2020	Q14 of the ICH: Public consultation
June 2021	ICH Q14: New guidelines are recommended to harmonise the scientific approaches to analytical method development based on a survey of pharmaceutical companies.

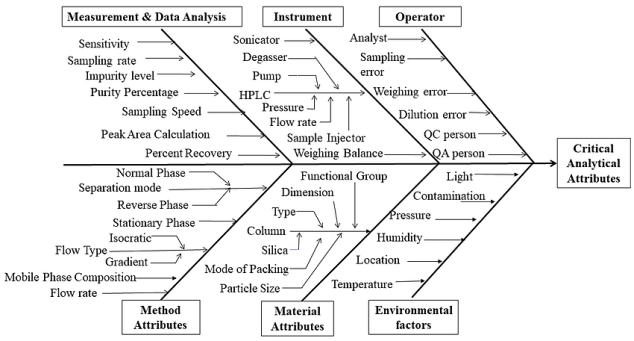

Fig. 2: Ishikawa Fish Bone Diagram

REGULATORY STANDPOINTS ON ANALYTICAL QUALITY THROUGH DESIGN [27]

The essential axioms of QbD revolve around a complete knowledge of a process, product, or purpose that has been specified prior to the start of a process. Quality by Design (QbD) has become an essential idea for the pharmaceutical business since it was first introduced by the United States Food and Drug Administration (FDA) in its "Pharmaceutical cGMPs for the twenty-first century [28] ."Previously, until 2005, the US Food and Drug Administration (FDA) required manufacturers to provide chemical, manufacturing, and control (CMC) information as part of a new drug application (NDA). The ICH Q8, Q9, and Q10 guidance documents, on the other hand, imposed stricter requirements for meeting a drug product's quality standards. Although the ICH Q8 (R2) guideline has not primarily addressed the analytical method development perspective in the context of design space, it has been extended to MODR with the goal of on-going improvement in method robustness for enhanced analytical comprehension. Adopting AQbD as a control method during the production process would, as a result, ensure process performance and product quality [29].

The implementation of AQbD is expected to strengthen the concept of "right analytics at the right time," which has enormous potential in drug product development. The reliance of pharmaceutical development and manufacturing on reliable analytical data demonstrates the value of QbD-guided analytical method development as the current domain of attention and implementation. Recent FDA

approvals of AQbD-supplemented NDA applications tend to stimulate and emphasise the importance and use of QbD in analytical method development. The USFDA and USP require system appropriateness assessment for an analytical technique in order to ensure continuing functioning of an analytical system and related methodologies. The USFDA and USP require system appropriateness assessment for an analytical technique in order to ensure continuing functioning of an analytical system and related methodologies. However, recent modifications to the USP - NF and European Pharmacopeia have allowed for flexibility in changing analytical techniques without requiring revalidation. There is currently no regulatory guidance dedicated to the systematic development of analytical methods. The next ICH Q14, "Analytical Procedure Development," as well as the revision of the ICH Q2 (R1) Guidelines on Validation of Analytical Procedures: Text and Methodology are encouraged to provide analytical technique validation criteria that match the ATP standards.

POTENTIAL APPLICATIONS OF ANALYTICAL QUALITY BY DESIGN IN ANALYTICAL SETTINGS

With the rising desire for the incorporation of systematic techniques and quality tools into analytical science, the popularity of AQbD has spread to numerous domains of analytical testing[30]

Analytical method development[31]

Several literature reports have been published on the application of AQbD for developing analytical high performance liquid chromatography (HPLC)[25] , ultra performance liquid chromatography (UPLC), high performance thin layer chromatography (HPTLC), liquid chromatography mass spectrometry (LC - MS), vibrational " spectroscopy, atomic absorption spectroscopy, electrophoresis methods, and many more. For the estimate of various medications or during the concurrent estimation of bulk pharmaceuticals and pharmaceutical dose forms the use of AQbD aids in the identification of highly influential factors (i.e... CMPS) from a variety of technique parameters such as mobile phase ratio, organic modifiers, and pH. Buffer strength, flow rate, injection volume, column type, dimension, all have a significant impact on CAAs to increase method robustness and performance.

According to the FDA, analytical techniques and methods are critical in the QbD paradigm, and real-time release testing and unconventional testing approaches give vital information for in-process control and improvement. Implementing QbD provides an opportunity to attain regulatory flexibility, but it demands a high level of resilience, product quality, and analytical method expertise. It is recommended to use a suitable design of experiments (DOEs) procedure in the AQbD approach to establish a validated MODR for a high degree of process-product-analytical method understanding. When compared to traditional methodologies, the adoption of AQbD workflows speeds up method development[32].

Bio analytical method development

AQbD concepts have been employed in the development of bio analytical methods for enhancing extraction recovery while chromatographic separation of analytes from biological fluids such as plasma, serum, lymph, tissue, and organ extracts. Many processing conditions, such as the nature of the extracting solvent, the extraction time, the centrifuge type, the centrifugation speed, the time and temperature, and the sample filtration procedure, all have an impact on the recovery process, and AQbD can assist in risk-based monitoring of the conditions to improve process efficiency. QbD for various analytical methods[33] such as:

1. HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals).
2. Karl Fischer titration for moisture content determination.
3. Vibrational spectroscopy, such as the UV technique, is used to identify and quantify chemicals.
4. LC-MS and other hyphenated techniques
5. Mass spectroscopy, UHPLC, and capillary electrophoresis are examples of advanced procedures.
6. An examination of a genotoxic contaminant.
7. Dissolution research
8. Biopharmaceutical methods

AQbD-based methodology, on the other hand, leverages a statistically planned experiment to address the design space completely and allow the experimenter to visualise and quantify all important variable effects[34] .Unlike current methodologies, the analytical quality by design (AQbD) approach minimises the number of out-of-trend (OOT) and out-of-specification (OOS) outcomes[35] .

Analytical Qbd Method Validation

QbD can also stimulate the employment of novel techn2ology and new approaches to process validation, such as continuous quality verification[36] . The AQbD method validation[37] methodology is that the validation of analytical method across a variety of distinct API batches. It employs both DoE and MODR expertise to create method validation for all types of API manufacturing changes that do not require revalidation[38] . The technique includes the ICH validation aspects as well as information on interactions, measurement uncertainty, control strategy, and continual improvement. This approach takes fewer resources than the usual validation approach while maintaining quality[39] .

IDENTIFICATION OF IMPURITIES AND DEGRADATION PRODUCTS

Impurity profiling and identification of degradation products in bulk drugs and finished products are highly essential for maintaining product quality, safety, and efficacy. Requirement of a highly sensitive analytical method along with critical monitoring of chromatographic conditions, in this regard facilitate estimation of impurities and degradation products, and controlling their levels within the acceptance limits for regulatory approval[40]. QbD concepts can also be applied in developing an appropriate control plan[41].

NON-DESTRUCTIVE PHARMACEUTICAL ANALYSIS[42]

Use of non-destructive tools is gaining high importance for saving time during pharmaceutical analysis of drug substances in bulk and finished products. New - Age spectroscopic techniques such as near infra-red and Raman are used for non-destructive analysis to identify impurities or counterfeit drug analysis for the purpose.

CONCLUSION

As a relatively new concept to analytical scientists, AQbD possess implicit challenges for implementation, particularly when it is not a strict regulatory requirement. There is no expectation of technology transfer or method validation, so a paradigm shift from traditional information-rich dossiers to scientifically sound and knowledge-rich documents is expected. Furthermore, worldwide harmonisation of AQbD terms and ideas, such as MODR, ADS or PAR, and ATP or QTMP, is required. Another problem in effectively harvesting QbD principles in the analytical arena is training human resources at the industrial and regulatory levels, necessitating specific criteria on recording of knowledge gained during method development. By using AQbd, the analytical technique makes it easy to acquire the optimum values, making further drug analysis easier. The present article is a humble attempt on our part to give essential yet comprehensive information on the growing concept, to strengthen existing comprehension of the concept, and to provide the required boost toward its fruitful implementation in the pharmaceutical environment. In many ways the success of companies in the near future may be a direct by-product of their ability to integrate the concepts of QbD. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company's strategy.

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