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Approach of analytical quality by design and regulatory need

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***Abstract*---**This paper gives idea about the Pharmaceutical Quality by Design (QbD) and describes use of Quality by Design to ensure quality of Pharmaceuticals. Quality cannot be tested into products but quality should be built in by design. The concept of QbD can be extended to analytical methods. The emphasis of AQbD approach is on understanding of the operation and the variables affecting Analytical Methods employed in product development. The variables which affect the output are identified and subjected to thorough risk assessment employing various tools and techniques discussed in the article, after which the variables are optimized. The final method is validated and a control strategy is put in place. Pharmaceutical firms increased the number of product development by using scientific tools such as QbD (Quality by Design). ICH Q11 guidelines clearly discussed QbD approach for API synthesis with examples. It is a current trend among pharmaceutical industry to implement analytical quality by design (AQbD) in method development process as a part of risk management, pharmaceutical development, and pharmaceutical quality system (ICH Q10). QbD has its perspectives to contribute the drug design, development, and manufacture of high-quality drug products. In the present review basic consideration of the QbD approach, its historical background, and regulatory needs are discussed.

***Keywords*---**Quality, Regulation, ICH, Robustness, Risk management.

Introduction

Recently FDA has approved few new drug applications (NDA) applying QbD approach to analytical techniques namely “Analytical Quality by Design”, like

HPLC and UV spectrophotometry in which regulatory flexibility has been granted for movement within the defined method operable design region (MODR)[1]. This approach will reduce the number of out of specification (OOS) and out oftrend results (OOT) hence provide base to constructsix-sigma approach in pharmaceutical products.International Conference on Harmonization (ICH) Q8(R2), ICH Q9 guidelines specified analytical targetprofile (ATP) for identifying MODR by analytical quality by design (AQbD) approach [2]. ATP is a prospective summary of measurement requirements that ensure that the method is fit for the purposewhere as MODR is based on multivariate approach toevaluate the effects of various method. In accordance to FDA requirement from 2013,MODR needs to be conducted together with method validation[3]. But a conference on AQbD by FDA in 2014, the current (OFAT) approach in method development phase is not an appropriate method approach for routine analysis to be considered under regulatory flexibility[4].Unlike usual method in literature, here first quality target product profile (QTPP) has been used to identify CQAs of the product [5]. Here QTPP determines the quality of the product, which helps us to define targetted responses to be optimized in life cycle of the product. Based on CQAs, Analytical target profile (ATP) was designed with accuracy, precision, specificity, linearity were selected as method performance characteristics for assay(Q-parameter)[6].

Quality by Design is the modern approach for quality of pharmaceuticals. This paper gives idea about the Pharmaceutical Quality byDesign (QbD) and describes use of Quality by Design to ensure quality of Pharmaceuticals[7]. The Quality by Design is described and some of its elements identified. Process parameters and quality attributes are identified for each unit operation. Quality cannot be tested into products but quality should be built in by design [8]. It includes the Quality target product profile, critical quality attributes and key aspects of Quality by Design. It also gives comparison between product quality by end product testing and product quality by Quality by Design. The foundation of Quality by Design is ICH Guidelines. It is based on the ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for pharmaceutical quality systems. It also gives application of Quality by Design in pharmaceutical development and manufacturing of pharmaceuticals [9].

The aim of pharmaceutical development is to design aquality product and its manufacturing process to consistently deliver the intended performance of the product. 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[10]. Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful. Design space is proposed by the applicant and is subject to regulatory assessment and approval [11].

Even though the pharmaceutical industry has focus on quality, it has failed to keep up with other industries in terms of manufacturing efficiency and productivity.

Quality-by-design (QbD) is a systematic approach to drug development, which begins with predefined objectives, and uses science and risk management approaches to gain product and process understanding and ultimately process control. The concept of QbD can be extended to analytical methods [12]. The emphasis of AQbD approach is on understanding of the operation and the variables affecting Analytical Methods employed in product development and hence creating an extensive knowledge repository. The variables which affect the output are identified and subjected to thorough risk assessment employing various tools and techniques discussed in the article, after which the variables are optimized [13].

QbD has gain importance in the area of pharmaceutical processes like drug development, formulations, analytical method and biopharmaceuticals. The main reason behind adoption of QbD is the regulatory requirements[14].Analytical Quality by Design (AQbD) plays a key role in the pharmaceutical industry for ensuring the product quality. The outcome of A QbD is the understanding from product development to commercial production. AQbD tools are ATP, CQA, Method Optimization and Development with DoE, MODR, and Control Strategy with Risk Assessment, Method validation, and continuous improvement[15].

There is much confusion among pharmaceutical scientists in generic drug industry about the appropriate element and terminology of quality by design[16]. The purpose of this paper is to discuss the pharmaceutical Quality by Design (QbD) and illustrate how it can be used to ensure pharmaceutical quality. The QbD is a systemic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure predefined product quality[17].Some of the QbD elements include: Defining Quality target product profile, Identifying critical quality attributes, link the drug excipients attributes, establishing design space, control strategy, and product life cycle management..A new approach to drug development could increase efficiencies, provide regulatory support and flexibility, and offer important business benefits throughout the product's life cycle[18]. This article explores the processes used in developing a market formulation and required supportive data, particularly in light of the industry's current movement toward submissions based on QbD. The work also facilitates the adoptionand implementation of QbD. principles in the development of pharmaceutical industries[19].[Successful implementation of QbD concepts requires cooperation across a multitude of company teams, from R&D to manufacturing to quality control and regulatory affairs. This is necessary to ensure that QbD concepts are incorporated not only when the first activities are initiated around aproduct's design but also during the design of the process used to make the product and other activities associated with a product'slife cycle. The application of the concept of quality by design (QbD) presented in this paper aligns with the principles of ICH Q8, Q9and Q10 guidelines[20].

Historical Background

In 2007 FDA received 5000 supplements, it was actually astriking raise in the number of manufacturing supplements to applications of New Drug Applications (NDAs), Biological License Applications (BLAs) and Abbreviated New DrugApplications (ANDA's)[21]. FDA recognized that there is an increase in lapse of NDA or ANDA submissions by the firms,large number of a supplemental application for every manufacturing change were received. In both original applications and supplements the data mainly focused was on chemistry. And the least attention was given on other important aspects of the manufacturing, such as engineering, product development[22].Eventually, the FDA acknowledged that more and more controls were required for drug manufacturing processes for efficient drug product and no doubt for better regulatory decision making. It resulted in more stringent regulatory upbringing. To solve this issue in 2002, the FDA implemented changes through the Pharmaceutical cGMP (good manufacturing practice) for the 21st Century. Expectations were mentioned in Process Analytical Technology (PAT) which is a system for designing, analysing, and controlling manufacturing processes based on understanding science and factors which affect the quality of final product[23].

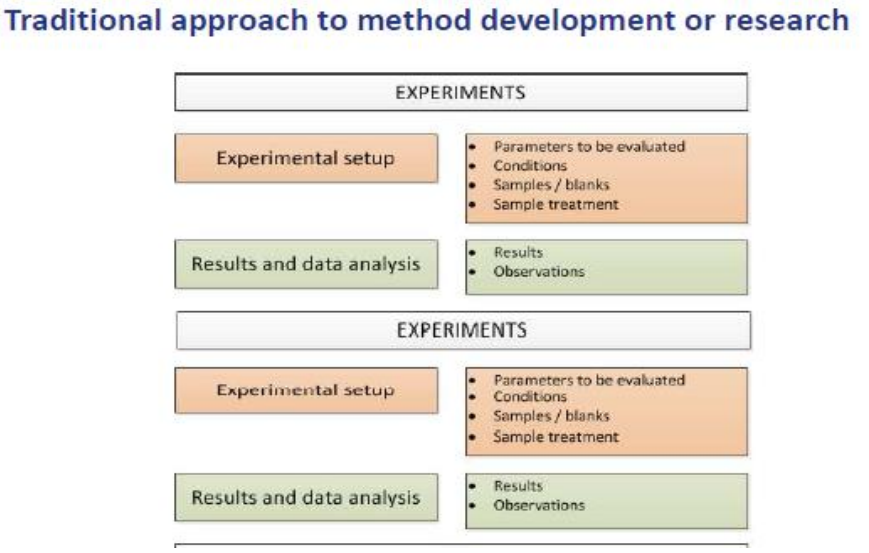
Year	Activities
1950	Operation Windows
1970	QBD created by Joseph M Juran
Sep 2002	QBD concept integrated by USFDA in cGMP
Sep 2004	USFDA release final report in Pharmaceutical cGMP
Sep 2004	For Innovative Pharmaceutical Development, Mnufacturing, and Quality Assurance
Nov 2009	ICH Q8(R2) Pharmaceutical Development
Nov 2005	ICH: Q9 Quality Risk Management
June 2008	ICH Q10 Pharmaceutical Quality System

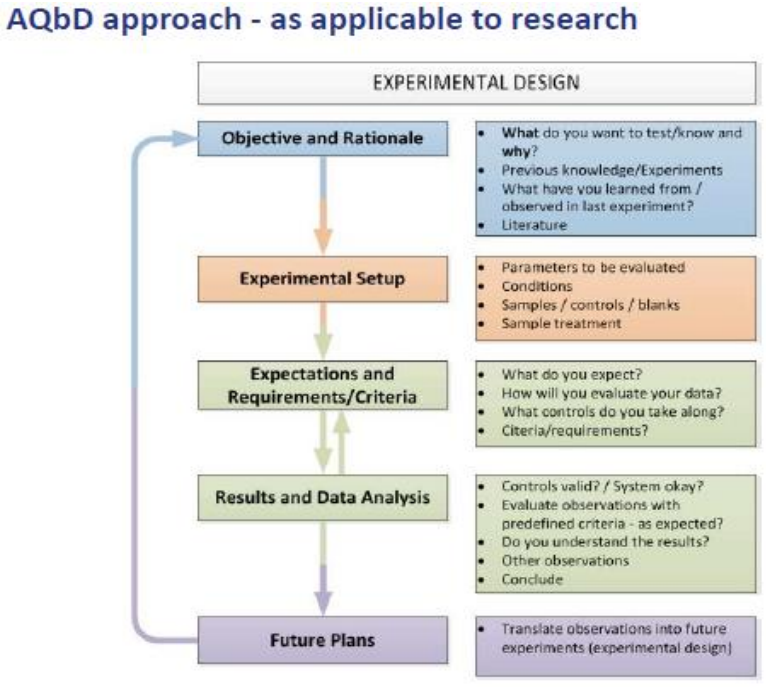
a. Benefits of QBD

The benefits of QbD involves 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. Eliminate batch failures, Minimize deviations and costly investigations. Avoid regulatory compliance problems, Smooth process of method transfer to the production level. QbD has gained importance in the area of pharmaceutical processes like drug development, formulations, analytical method and biopharmaceuticals. The main reason behind adoption of QbD is the regulatory requirements. Analytical Quality by Design (AQbD) plays a key role in the pharmaceutical industry for ensuring the product quality. The outcome of A QbD is the understanding from product development to commercial production[24].

b. Current Vs Traditional Approach of Qbd [25]





Regulatory aspect of QbD:

In 2005, the USFDA requested that participating companies submit CMC information demonstrating QbD application as part of a New Drug Application. QbD entails a full grasp of the process, as well as the definition of a goal or target

prior to the start of the process. Other characteristics for QbD implementation include design space and real-time release risk assessment. In its Q8 pharmaceutical development, Q9 quality risk assessment, and Q10 pharmaceutical quality system, an international conference on harmonisation was held.establishes high rules for product quality[26]. The FDA additionally emphasises the importance of pharmaceutical product quality by introducing Process Analytical Technology (PAT), a Framework for Innovative Pharmaceutical Development[27].

In a nutshell, efficient manufacturing processes can ensure product quality and performance. Specifications for products and processes are based on a scientific understanding of how process variables affect product performance [28.] Risk-based regulatory approaches are used to gain a scientific understanding of the product quality and performance process and to govern it. Modifications are made to related regulatory policies and actions.to take into account current scientific knowledge Quality control is a never-ending procedure[29].

The quality guidelines of the international conference on harmonisation, ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality System, explain the underlying principles of QbD, such as science- and risk-based product development, risk assessment, lifecycle approach, and method design[30].

Analytical method development employing the QbD methodology is a current topic of attention and needs to be applied as a result of the above-mentioned discussion. The process of creating and verifying analytical methods in parallel with product QbD helps product quality even more, with a high degree of confidence, and it may be used to improve product quality.to profit in the same way[31].The requirement for rigour in analytical method development and, progressively, an analytical QbD is becoming more important as pharmaceutical research and manufacturing become more reliant on reliable analytical data (AQbD). Although the ICH Q8 (R2) guidelines do not specifically mention analytical method development in relation to design space, it is acknowledged that the notion can be used to analytical design space and continual improvement in method robustness and understanding[32].

ICH guideline

Analytical procedures are an important aspect of the control approach in the pharmaceutical quality system (ICH Q 10 recommendations). As a result, implementing analytical QbD as a control approach in the production process will assure predetermined performance and product quality[33]. This covers facility, instrument operating conditions, final product specification, and associated procedures and frequency, as well as metrics and qualities connected to drug substance and drug product materials components. The use of AQbD is intended to reinforce the concept of "correct analytics at the right time," which is critical in the drug development cycle. A few months ago, the FDA approved a few new medication applications based on analytical QbD, emphasising the importance and benefits of QbD in the development of analytical methods[34].It stimulates the use of analytics in the product development cycle in order to better understand

drug excipient interactions and assess product quality. Critical quality attributes (CQA) are measured during the experiment, process, control, and continuous process verification to track product quality trends[35]**.**As a result of this resonance, the pharmaceutical sector has been drawn to the concept of analytical quality by design (AQbD). Despite the fact that cGMP rules have been in existence for over a decade, a large number of FDA QC-related warning letters have indicated that organisations have issues with risk management systems in analytical procedures and related systems.[36]**.**

Regulatory Challenges

"In a QbD approach, the regulatory burden is lighter because there are greater ranges and restrictions based on product and process understanding," Changes within these ranges and restrictions do not need to be approved in advance". Inspections have traditionally been carried out utilising the FDA's system-based approach and in line with the CDER's Compliance Program "Inspection of Licensed Bio-logical Therapeutic Drug Products"[37] However, the question now arises as to how the inspection will take place under the current situation where QbD is required The FDA inspection team will assess the implementation and effectiveness of the process design as described in the application, as well as whether knowledge and risk management have been successfully transferred from development to manufacturing, during prelicense or preapproval inspections under the QbD concept. Throughout the product lifecycle, the inspection will assess the quality system's efficacy in terms of consistent product quality, change in control methods, process improvements, deviation management, and knowledge and risk management [38.]Facility and equipment qualification and maintenance, as well as raw material screening and supplier management, will all be carried out as before. However, programmes that demonstrate robustness and consistency in design, testing, and monitoring would be recommended[39].

Roadmap for QbD implementation/ Elements of QbD
Analytical Target Profile

AQbD begins with the identification of an analytical target profile, or ATP, which is a QTPP analogue. The purpose of the analytical method development process is defined by ATP, which links the method's outcomes to QTPP. Once the regulatory authorities approve the ATP statement, it becomes a crucial parameter in AQbD, allowing for greater continual development of analytical methods and their selection. Internal change control management systems in the pharmaceutical business are responsible for the proper implementation of ATP to enable regulatory flexibility[40].

The ICH Q8 R(2) guidelines include ATP as a method for method development. It specifies the method requirements that should be measured. "ATP" stands for "a statement that describes the method's purpose and is used to guide method selection, design, and development activities."Method requirements such as target analytes (product and impurities), analytical technology category, and product characteristics must all be selected. An first risk assessment would be carried out in order to prepare for the future[41]**.**

In other words, ATP identifies the method's goal, which leads to method selection, design, and development. To create the ATP, you must first define the method characteristics that will serve as indicators of method performance, as well as the combination of all performance criteria required for the analytical application. The ATP specifies what the method must measure (acceptance criteria) and to what extent it must be measured (i.e., performance level characteristics, such as precision, accuracy, range, sensitivity, and the associated performance criterion**)[42].**

Characteristics of Analytical Method Performance

The performance parameters of analytical methods are defined to suit the requirements of the analytical target profile. Method performance can be divided into two categories.There are systematic (bias) and random (variance) components. In general, the effectiveness of an approach is determined by both. Many validation factors for chromatographic separations have been published by USP and ICH, and are considered method performance characteristics[43].Accuracy and precision are two of these metrics that are frequently considered as technique performance qualities for quantifying the material. It is thought that without proper specificity, linearity, and peak resolution, no approach can be accurate and exact. These performance metrics, however, do not represent the method's resilient behaviour. Range is another crucial component that must be established based on acceptable performance qualities, both systematic and random[44].Robustness refers to the operational range of technique parameters that can be used to produce specific results. A statement of accuracy and precision, for example, should be included in an ATP assay, but not necessarily linearity and specificity[45]**.**

Critical Quality Attributes

Method properties and method parameters are included in CQA for analytical procedures. CQA is distinct for each analytical procedure. Method properties and method parameters are included in CQA for analytical procedures[46]**.** A CQA is a physical, chemical, biological, or microbiological property or characteristic that must be within an appropriate limit, range, or distribution to provide the required product quality, according to ICH Q8 R2. CQAs are a type of quality assurance.Drug substance, excipients, intermediates (inprocess components), and drug product are all frequently connected[47].

CQAs are often created from the Quality Target Product Profile and/or existing information, and they are then used to steer product and process development[48].
In the case of biotechnological/biological goods, the majority of the drug's CQAs are linked to the drug substance and are thus a direct result of the drug substance's design or production process. Impurities are a type of possible pharmacological substance CQA that is often overlooked[49]. A quality trait that must be kept within predetermined limitations to guarantee that the product's intended safety, efficacy, stability, and performance are met[50].

Risk Assessment

Risk assessment is a science-based technique that can discover material qualities and method parameters in quality risk management (ATP). Risk assessment can be done at any stage of the method development process, from the beginning to the end. The AQbD strategy entails identifying risks early in the development process, then developing appropriate mitigation measures and management strategies[51].

AQbD focuses on a detailed risk assessment of the factors that could cause variability in the method, such as analyst methods, instrument configuration, measurement and method parameters, sample characteristics, sample preparation, and environmental conditions, once the technique has been identified[52].Analytical QbD necessitates the risk assessment stage before method transfer and throughout the product life cycle, whereas traditional method development was centred on evaluating the technique after transfer. The ICHQ9 guideline defines risk assessment strategy as "a systematic method for the assessment, control, communication, and review of quality risks throughout the product lifetime"[53]

The first phase, Risk Identification, is critical for identifying and prioritising potential threats. These risks could include instrument operation, reagent properties, cycle time, and so forth. In the event that the primary approach fails, it is usually a good idea to devise a backup plan. Risk factors are identified using flow charts and check lists[54].The Ishikawa Fishbone Diagram and the CNX method are two tools used in this step. The Ishikawa Fishbone diagram, also known as the Cause and Effect diagram, divides risks into several groups based on their source[55].

It is usually done by Relative Risk Matrix Analysis and Failure Mode Effect Analysis.In the RRMA, the risk variables are categorised asHigh, Medium and Low-Risk Factors, such as Methodology for Sample Preparation. During the Method Development process, these will be addressed. Noise Factors. The variables with low and medium risk variables are accepted and do not needs further investigations, where as the high risk variables are unacceptable and needs to be optimized to reduce its effects on the method performance[56].

The FMEA, involves the rating of the Risk factorsbased on Severity Occurrence Detectability, on a scale of 1-5,where Severity is the effect on the patient related to safety and efficacy (CQAs), Occurrence is the chance of failure related to product, process knowledge, and control, and Detectability is the analytical method's and sampling's ability to detect a failure[57].Risk is typically believed to be the sum of the likelihood of harm and the severity of that harm. Risk assessment aids in the improvement of method or process qualityA risk assessment is beneficial for successful communication between the FDA and industry, as well as between research and development and manufacturing, as well as across multiple manufacturing sites within a corporation[58].

After you've identified the technique, you can move on to the next step.AQbD focuses on a thorough risk evaluation of aspects such as analyst methodologies,

instrument design, measurement and method parameters, sample characteristics, sample preparation, and environmental circumstances that could cause method variability[59]. Analytical QbD requires the risk assessment stage before method transfer and throughout the product life cycle, whereas traditional method development depended on testing the technique after transfer[60].

Product Design Space

According to the ICHQ8 recommendations for "design space" in product development, a method operable design region (MODR) can be formed during the method development phase, which could serve as a source for a reliable and cost-effective method. MODR is the operating range for the critical method input variable (equivalent to CQAs) that consistently generates results that fulfil the ATP goals. MODR allows for flexibility in various input method parameters, resulting in the expected method performance criteria and method response without having to resubmit to the FDA[61]. It uses a multivariate, risk-based, science-based methodology to assess the influence of numerous factors on method performance. The FDA recommends that MODR be done in conjunction with method validation. Once this has been established, the most appropriate procedure should be used.controls can be put in place and method validation can be carried out. Many analytical papers have been published that use factorial or fractional factorial design or response surface methods as the experimental design. However, such efforts were confined to the creation of mathematical models that link input variables (Xn) with output responses (Yn)[62].

DoE can be used to confirm and refine critical method variables based on statistical significance once the potential and crucial analytical method variables have been determined with the initial risk assessment. It can be calculated per unit operation or as a result of a combination of many technique variables and their interactions and reactions (critical method attributes). This method is ideal for screening a large number of conditions obtained from a small number of tests. Then, employing statistical tools, data evaluations are quite important.It's crucial to determine vital method variables as well as the best method variable ranges for obtaining a sturdy region for the critical method features[63].

To guarantee that maximum insight is acquired while limiting the overall number of experiments, robustness experiments are often performed on parametric variables using Design of Experiments (DoE). Surrogate measures of attributes such as accuracy or precision may be evaluated depending on the type of technique[64]. Process robustness, according to ICH Q8, is described as "the ability of a process to accept variability in materials and changes in the process and equipment without compromising quality." The qualities of the starting materials will influence the robustness, impurity profile, physicochemical attributes, process capability, and stability of the medicinal substance synthetic process. Understanding the process will provide enough information to establish robustness.parameters by comparing and contrasting different operational settings, scales, and equipment[65].

MODR was utilised to create a routine operational region (e.g., analysis time, procedure and limits). According to the ICH Q8 recommendations for "design

space" in product development, a method operable design region (MODR) can be formed during the method development phase, which could serve as a source for a reliable and cost-effective method. Understanding method performance zones aids in determining the desired outcome.operational circumstances[66]. The sensitivity of critical technique parameters and analytes should be assessed. MODR is the operating range for the critical method input variable (equivalent to CQAs) that consistently generates results that fulfil the ATP goals. MODR allows for flexibility in various input method parameters, resulting in the expected method performance criteria and method response without having to resubmit to the FDA. It uses a multivariate, risk-based, science-based methodology to assess the influence of numerous factors on method performance[67].

Control Strategy

Control strategy is a pre-determined set of controls based on analyte type and MODR knowledge. The whole statistical data obtained during the DoE and MODR stages, as stated above, can be used to develop a method control plan. Correlations between technique and analyte properties for the capacity to meet ATP criteria can be drawn using this statistical experimental data. The inconsistency in method parameters will be resolved by using a control technique (e.g., reagent grade, instrument brand or type, and column type). When comparing the AQbD methodology to the traditional approach, the method control strategy does not appear to be significantly different. To ensure a tighter link between the method purpose and performance, method controls are constructed based on CQA, DoE, and MODR experimental data[68].

The control strategy for product QbD is meant to ensure that the product is produced quickly and to the required quality. The control strategy is drawn from a variety of sources.The data was gathered during the technique development and verification phases. This data correlation will anticipate a method's ability to meet ATP criteria and control strategy, as well as the overall monitoring of method parameters that have a substantial impact on method performance (variability). It should be noted that the AQbD approach's method control strategy is identical to the traditional control strategy[69].

It is critical that the set method functions as expected and consistently produces accurate results; hence, method control is necessary. A factor that has been identified as posing a risk must be managed. The high-risk elements are given more attention. Controlling the system allows you to assess and verify its applicability at any moment[70].

If the risk is minimal and controllable, a method control plan may be created, which typically entails doing an appropriate system suitability check and having control over it from time to time to ensure that the method delivers the desired method attributes. Surprisingly, the AQbD control approach is very similar to the classic control strategy.[71]

Throughout the course of a product, both the manufacturing process and the method are likely to change due to inadvertent deviations, continuous improvement operations, or the desire to improve.In a different setting, use the

method and/or procedure[72]**.** This stage's purpose is to ensure that the optimised method regularly performs as expected. This step entails the eventual replication of optimised experiments, as well as data gathering and analysis, to ensure that the method remains in a controlled state. To ensure that the technique functions as intended, a continuous trend of collecting and analysing data on method performance should be developed[73]**.**

Process Monitoring, Life Cycle Management and Continous Improvement

Management of the Lifecycle Method validation, verification, and transfer are the main activities that assure the method's fitness for its intended use, even after passing through all of the aspects of QbD for a particular analytical method. When these factors are combined, the result is 'lifecycle management of analytical procedure,' which begins with the creation of ATP and continues until the technique is in use. The main focus for performance qualification, such as precision studies on the site of routine use, is the resultant confirmation with respect to ATP. Continual verification entails operations that ensure that the method is under control at all times during its lifecycle[74]**.**

A Control Approach for Implementing Design Space at the Commercial Stage is Life Cycle Management

CMM is the last step in the AQbD life cycle; it is a never-ending process of sharing information obtained throughout development and testing.design space implementation This incorporates risk assessments, prior knowledge assumptions, statistical design considerations, and a link between the design space, MODR, control strategy, CQA, and ATP. Once a technique has been validated, it may be used for routine purposes and the performance of the method can be tracked over time. Control charts, tracking system appropriateness data, method-related research, and other methods can be used to accomplish this. CMM enables the analyst to identify and correct any out-of-trend behaviour in advance[75]**.**

This comes after the establishment of an analytical technique for quality control or routine testing, which is accomplished by tracking the method's performance over time to ensure that it meets the ATP criteria. Control charts or other tools are used in the pharmaceutical business to track system appropriateness data and method-related research[76]. The method validation, verification, and transfer are the important phases that assure the method's fitness for its intended application when going through all of the parts of AQbD for a specific analytical method. The process of combining all of these elements is known as 'lifecycle management of analytical procedure,' and it begins with the creation of ATP and continues until the methods are in use. The major objective of performance qualification, such as precision investigation at the site of routine usage, is the subsequent confirmation with respect to ATP Method Installation Qualification activities (including knowledge transfer) will be required when a method needs to be transferred to a new location[77]**.**

Selection Of Doe
Screening

In screening, qualitative input variables can be screened out. It identifies the various critical method parameters (CMP) to be considered in the optimization experiments. In addition, it also works as a semi optimization tool to indicate the required levels of CMA for an optimization experiments. The various tool and selection approaches are shown in Table 4.The screening experiments should conclude the segregation of CMP that need to be either controlled or subjected to DOE techniques in MODR optimization[78].

Optimization

In this stage, quantitative measures for critical method in variables (i.e., CMP) either from screening or directly from risk assessment can be incorporated. It provides a base for scientific understanding of relation between quantities of input variables (CMP) and output response which will show considerable effect on method performance and ATP[79]**.**

Selection of DOE Tools

During the optimization, many approaches can be used to derive a mathematical relationship (model).The decision on selection of tool for DoE has to be made based on the number of input variables, knowledge on controlled parameters, and scientific understanding between result and variable (if any). Statistical knowledge is prime importance to interpret the interaction and contribution of variables (Xn) in method responses (Yn), serving as a tool to select the variables at optimum levels. For example, if the effect of all input variables and their interactions are to be measured, factorial design can be applied then it can be considered and optimized with RSM (response surface methodology). Taguchi method can be used with lower number of experimental runs compared to factorial designs (say, 50%, 25%, etc.) but the interactions confounded need to be resolved. Where large numbers of input variables are to be studied without interaction effects, Plackett- Burman methods can be used. A typical selection of techniques is shown in Table 4[80]**.**

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Method Operable Design Region (MODR) and Surface Plots

The contour plot is a 2D response plot representing the impact of pH (x axis) and % aqueousphase (y-axis) on retention time of analyte, whilst factors likeflow rate and other instrument configurations are controlled.Numbers like −1, −2, +1, and +2 in both axes represent the coded level of variables used in DOE plan.[83]
This contour is suitable for the response if it is nonlinear and the relationship between input variable and method response is having more curvature effect. Then MODR can be selected from contours using mathematic models. The predicted value of method response can be verified by using actual experimental run as a part of model validation.There is another surface model that can be obtained by means of simulation that provides the change of response with respect to variables, which is more suitable for linear relationship .

Model Validation

Prior to the choice from contour or graph, the predicted values for the targeted method response have to be validated by actual experimental run. Then the regression analysis has to be carried out to validate the model statistically.

Method Design Output

A set of method conditions will have been developed and defined which are expected tomeet the ATP.Those conditions will have been optimized based on understanding of their impact on method performance. QbD-based treatment of the robustness of an analytical method requires the assessment of all parameters (factors) which most strongly influence selectivity (results) alone and in combination. The experimental verification of many factors simultaneously is impractical and associated with extreme technical difficulties and expense. Some authors, have employed statistical studies, such as Plackett-Burman or fractional

factorial designs and risk-based approaches [16– 20] to overcome the challenge and reduce the experimental workload. Other procedures include running automated robustness experiments [21–24]. The present paper, however, employs statistical analysis that is principal component analysis which exhibits factor extraction of variable parameters toevaluate robustness.[84]

Current Status of Qbd as it Relates to the Use of Methodological Approaches in Pharmaceutical Development and Quality Control

Scope of AQBD in analytical method development.
With the commercial manufacturing of product it is important that the analytical method is time saving as well as robust and accurate since the release in market is decided on final quality control results of finished product accompanied by other datas of the batch. The main concern of the analytical chemist is to develop a suitable analytical method that the exactly works as per the intended use. In current scenario of analytical chemistry, there are two approaches followed for any analytical method development. The former is based on the trial and error method which studies one factor at a time where one parameter alone is optimized for the expected response whilst others remained constant. This practise yields a narrow robust behaviour of the method for instrumental variables used in method development. Hence, the strategy of one factor at a time has high risk in method failure and always requires revalidation protocol after method transfer or during method development.

The later approach is Analytical Quality by Design (AQbD) which explores scientific understanding in method implementation sequences and starts with product quality that relates the risk assessment in method choice and then between method parameter and expected method results and finally a region for high robust and cost effective approach. Design of Experiment (DoE) is a part of AQbD, and it represents the interaction among the input variables that ultimately affect the method response and results. AQbD paradigm is a preferred and recommended strategy to be followed in analytical method development so as to attain regulatory flexibility and reduce Out of specification (OOS), Out of term (OOT) and Out of control (OOC) results and when this approach is used to study any chromatographic method, the methods explores more knowledge of the parameters that has to be controlled and monitored during the life cycle of the method.

Conclusion

The goal of a well-characterized method development effort is to develop a reliable method that can be demonstrated with a high degree of assurance to consistently produce data meeting predefined criteria when operated within defined boundaries.

The QbD process on an active partnership of analytical scientists at both the development and operational laboratories as methods are developed and as factors that lead to potential method failures are identified and controlled. The main reason behind adoption of QbD is the regulatory requirements. Analytical Quality by Design (AQbD) plays a key role in the pharmaceutical industry for

ensuring the product quality. The outcome of A QbD is the understanding from product development to commercial production. AQbD tools are ATP, CQA, Method Optimization and Development with DoE, MODR, and Control Strategy with Risk Assessment, Method validation, and continuous improvement. The application of QbD concept to analytical method is justifiable, because many variables significantly affect the method results which include instrument settings, sample characteristics, method parameters, and choice of calibration models. Being chromatographic technique is the most common analytical tool in pharmaceutical quality control, and the number of variables involved in analytical method development phase is almost equivalent to the number of variables involved in formulation and development protocols for dosage form so implementation of QbD provides an opportunity to achieve regulatory flexibility but requires high degree of robustness, product quality, and analytical method understanding**.**

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