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Review Article

Analytical Quality by Design (AQbD) : A New Horizon For Robust Analytics in Pharmaceutical Process and Automation

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Abstract

The apprehension and criticism on the quality and reliability of pharmaceutical products has augmented substantially in recent times, ensuing the regulatory bodies affirming the necessity of systematic principles for drug development. ICH has instituted series of guidelines such as Q8, Q9, Q10 and Q11, all of them stressing on the implementation of systematic approaches of Quality by Design (QbD) and Process Analytical Techniques (PAT) for pharmaceutical product and process design. QbD has earned plentiful consideration by formulation developers, the approach with sound scientific knowledge and early risk assessment is been accepted as an integral and imperative part of pharmaceutical dosage form development, relishing the benefits of risk assessments on early sage and design space on the later stage of product life cycle. However, the idea, reference, guidance and way of practicing QbD in the analytical field termed as AQbD are limited wherein no concrete regulatory requirement have been spelt out yet. In this article, the key milestones of QbD such as Critical Material Attributes (CMA), Quality Target Product Profile (QPP), Critical Quality Attributes (CQA), Critical Method Parameters (CMP) and the guidance for the effective Design of Experiments (DoE) differing form the conventional One Factor At a Time (OFAT) methodology has been explained. Unlike current methods, methods developed using AQbD approach reduces the number of Out of Specification (OOS) and Out of Trend (OOT) results due to robustness of the method within the Method Operable Design Region (MODR).

Keywords: AQbD, PAT, MODR, DoE, ATP, CMC, CQA, QTPP, FDA, Risk management

INTRODUCTION

Quality by Design (QbD) has become an important concept for the pharmaceutical industry which has been further defined in the International Conference of Harmonization (ICH) guidance on Pharmaceutical development as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process monitoring and control, based on sound science and quality risk management". It is a way for the industry to share pharmaceutical dosage form development and manufacturing information with regulators leading to regulatory decisions based on scientific and risk management principles.

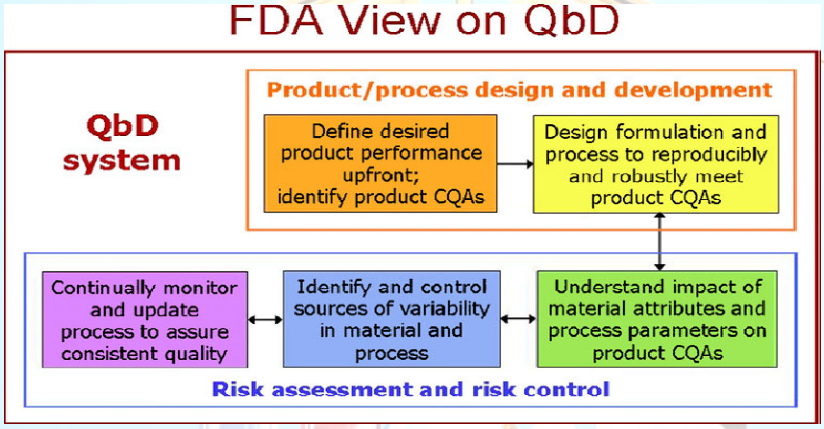
At present, in generic drug development QbD continues to be a major goal in CDER's (Council for Drug Evaluation and Research) ongoing drug quality initiatives and implementation is moving forward in CDER's office of Pharmaceutical Science. "Technologies such as PAT are crucial to implementing the knowledge gained from quality by design in a meaningful and efficient way…" as stated in one of the directives issued by the office of CDER.

There were few scientific conferences during the late 2013 and early 2014 organized by FDA, insisting on the implementation of the existing QbD concept to analytical method development (AQbD). Several researchers reported that similar opportunities exist for applying QbD to analytical methods as they do for the manufacturing processes. AQbD helps in development of a robust and cost effective analytical method which is applicable throughout the lifecycle of the product, to facilitate the regulatory flexibility in analytical me-

thod. The broad knowledge obtained from the process is used to establish a method operable design region (MODR), a multidimensional space based on the method factors and settings that provide suitable method performance. It is also used to establish meaningful method controls of which system suitability is one component.

Differences between conventional approach and QbD approach is as shown below in Table-1

Conventional approach	QbD Approach
Quality is assured by testing and inspection.	Quality is built into product & process by design and based on scientific understanding.
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, any specifications are based on batch history.	Here, any specifications based on product performance requirements.
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.



DEFINITION OF AQbD- QbD principles when applied to the development of analytical methods is coined as "AQbD". Analogous to process QbD, the outcome of AQbD is a well understood, fit for the purpose, and robust method that consistently delivers the intended performance throughout its lifecycle.

BENEFITS OF AQbD APPROACH TO ANALYTICAL METHODS:

(i) Methods will be more robust and rugged, resulting in fewer resources being spent on the investigation of OOS results and greater confidence in analysis during the entire product testing life cycle.

(ii) The knowledge derived from the complete AQbD cycle would be an easy and ready reckoner during the investigation of OOS results.

(iii) Introduction of new analytical methods – from R&D to QC Lab – using AQbD approach will lead to a faster and higher transfer success rate vis-a-vis the traditional technology transfer approach.

(iv) No requirement of analytical method re-validation within the MODR

(v) AQbD would be the driving force to ensure all analytical methods work right first time and every time in the pharmaceutical world where

lean and six sigma methodologies are deployed extensively.

(vi) More focus would be given to how well the method would perform at everyday, "real world" operating condition rather than the traditional approach of "checkbox tick mark" for the regulatory compliance.

Table-2 provides a bird's eye view on the comparison between analytical methods developed through traditional approach vis-à-vis the AQbD approach.

CORRELATION OF QbD and AQbD

In table-3, the different components of QbD and AQbD have been chalked out and correlated to put forth a better understanding of the synergy between the two domains.

As of today, pharmaceutical industries have many questions and require a lot more discussions on the implementation of AQbD and its correlation with other components of pharmaceutical quality systems. Literature survey reveals that many researchers have adopted QbD principles to the development of analytical methods. Certainly, most of the works were not enough to define the way of implementation of AQbD, because people felt that implementation of DOE in analytical method is QbD and it is incorrect. Moreover these reports have reflected the inadequacy of knowledge on analytical target profile (ATP), method performance characteristics, risk assessment, choice of DoE tool in AQbD process, optimization of MODR region and its verifications and so forth.

We know that system suitability testing (SST) for analytical method is required by USP and FDA to ensure ongoing performance of an analytical system and relevant methods. Very recently related chapters have been updated by United States Pharmacopoeia (USP-NF) and European Pharmacopoeia (EP) in which flexibility is granted for an analytical method that can be changed without the need for re-validation if AQbD approach has been implemented. The USP chapter <1058> makes a statement that SST can substitute an instruments performance qualification; however further guidelines are not given. So there are many questions which still exist among regulatory expertise, and thus the concept of AQbD became a continuing interest to discuss and to learn more in the coming days.

REGULATORY PERSPECTIVE OF AQbD –

Reference to pharmaceutical quality system (ICH Q10), analytical method is key part of control strategy. Thus implementation of AQbD in manufacturing process automation, the control strategy will ensure predetermined performance and product quality. This includes parameters and attributes related to drug substance and drug product material components including the facility, instrument operating conditions, finished product specification and the associated methods and frequency. Implementation of AQbD is expected to strengthen the concept "right analytics at right time" which plays significant role in logical and scientific drug product development cycle.

Already, FDA has approved a few new drug applications based on analytical QbD and referred to the importance and benefits of QbD in analytical method development. It triggers the role of analytics in the product development cycle for understanding drug-excipient interactions and for the measure of critical quality attributes (CQA) during experiment, process, control and also continuous process verification in order to monitor trends and in turn maintaining the quality of the product consistently. Though cGMP regulations have been in space in the last one decade, the significant number of QC related warning letters issued by FDA demonstrated that companies have problem with risk management system in analytical methods in the absence of AQbD. Therefore, Quality assurance personnel believe that AQbD will be a better solution to avoid OOT and OOS and reduce the risk in method failures where the risk assessment is described logically and scientifically with risk mitigation plan.

ICH Q8 (R2) guidelines do not discuss analytical method development in correlation with design space; however it is understood that the concept can be applied to analytical design space and continuous improvement in method robustness and understanding. The lifecycle concept described in ICH Q8 is adaptable to analytical procedures if we consider an analytical procedure as a process and the output of this process as the reportable results, ie, the value that will be compared to the accep-

tance criterion. The purpose of applying lifecycle principles to analytical procedures is to holistically align analytical procedure variability with the requirements of the product to be tested and to improve the reliability of the procedure by understanding, reducing and controlling the sources of variability. Enhanced understanding of variables that affect the performance of an analytical procedure provides greater assurance that the quality attributes of the tested product can be reliably assessed. The lifecycle management process provides the framework for defining the criteria for and development of an analytical procedure that meets the acceptance criteria. Implementation throughout the procedure's lifecycle of change management process that is based on knowledge gained during the procedure's lifetime ensures that the procedure remains fit for its intended use.

Table -2

Sr.No.	Traditional approach	AQbD approach
1	Start with hit and trial approach to meet method intent	Start with pre-defined objectives (ATP)
2	Method performance evaluated during validation	Focus on performance through establishment of ATP
3	Limited understanding of analytical variables	Systematic evaluation of individual variables and interaction effects(s)
4	Method quality based on method validation	Performance qualification is the assurance of method quality
5	Method verification and transfer are separate exercises	Performance qualification and verification are continuous exercises throughout the life cycle
6	No regulatory flexibility with respect to changes	Working with the MODR would not be considered as change there by reducing post-approavl changes
7	No space for further improvement	Flexibility to implement continuous improvement

OFAT vs AQbD IN ANALYTICAL METHOD DEVELOPMENT

In present days, analytical method failure is becoming more common especially during method transfer as well in quality control departments during the product life cycle stage.

In the current practice, the implemented analytical methods are based on one factor at a time (OFAT), in which one parameter alone is optimized for the expected response while the other parameters are kept constant. This has always resulted in a narrow robust behavior of the method for instrumental variables used in method development phase. Hence, the current strategy OFAT for analytical method development has a high risk in method failure and would require revalidation protocol after method transfer or alternative method development, thereby increasing the cost of the method.

AQbD explores scientific understanding in method implementation sequences and starts with product quality that related the risk assessment in method choice and then in between method parameters and expected method results and finally a region for high robust and cost effective approach. DoE, is a part of AQbD and it represents the interaction among the input variables that ultimately affect the method response and results. At this juncture, AQbD paradigm is a preferred and recommended strategy to be followed in analytical method development so as to attain regulatory flexibility and reduce OOS, OOT, high degree of robustness and cost effective analytical method.

Table-3

Sr.No.	Formulation Qbd		Analytical QbD	
	Component	Objective	Component	Objective
1	Quality target profile (QTPP)	Define the type of drug delivery, system, dosage form, dosage design, pharmacokinetics, stability expectations of formulation	Analytical Target profile (ATP)	Defines what to quantify and how to quantify.
2	Critical Quality Attributes (CQA)	Define the physical attributes, identification, Assay, Dissolution, Impurity, profile requirements and other quality expectations	Critical Quality Attributes (CQA)	Separation, identification, accuracy, precision, robustness, ruggedness requirements
3	Critical Process Parameters (CPP)	Identifying the process parameters which could have impact on quality such as critical load level, agitation level, temperature, pH	Critical Method Attributes (CMA)	Identifying method parameters which could have impact on the performance of the method, such as buffer pH, column temperature, injection volume, organic solvent concentration etc
4	Critical Material Attributes (CMA)	Evaluating the criticality, type and grade of raw material used in formulation	Critical Material Controls (CMC)	Evaluating the reagents, reagents grades and concentrations used in the analysis
5	Design Of Experiments (DoE)	Nested or factorial design to identify a centre process and create a design space	Design Of Experiments (DoE)	Nested or factorial design identify a centre method and create a method design space
6	Process validation	Establishing practical proof that a process is reliably bringing quality products	Method validation	Establishing practical proof that the method is reliably bringing quality results
7	Control Strategy and Risk Management	Ensuring the product production with desired quality	Control Strategy and Risk Management	Ensuring the method performance with accepted results

IMPLEMENTATION OF AQbD

Implementation of AQbD provides an opportunity to achieve regulatory flexibility but requires high degree of robustness, product quality and analytical method understanding. To adopt a suitable design of DOE protocol in AQbD approach to identify a validated MODR for high degree of process-product-analytical method understanding is recommended. The stage wise implementation of AQbD in pharmaceutical quality system is pre-

sented in the diagram-

FLOW DIAGRAM OF QbD APPROACH TO AQbD

Target Measurement	Determine what to measure and where/when to measure it. Develop measurement requirements based on product QTPP and CQA
⚜	
Select Technique	Select appropriate analytical technique for desired measurement. Define method performance criteria.
⚜	
Risk assessment	Assess risks of method operating parameters and sample variation. Can use risk assessment tools (FMEA)
⚜	
Method development / validation	Examine potential multivariate interactions (DoE and design space). Understand method robustness and ruggedness
⚜	
Control strategy	Define control space & system suitability, meet method performance criteria
⚜	
Continual improvement	Monitor method performance ; update as needed as process and analytical technology evolves

Implementation of QbD in analytics is a parallel process to that of product QbD as shown below –

QTPP ⟷ ATP (Analytical Target Profile)

Design Space ⟷ MODR (Method Operable Design Region)

Initially, implementation of AQbD depends on the target measurement which comprises the product file in the form of ATP (Analytical Target Profile - It is the analogue of QTPP in product design) and CQA (Critical Quality Attributes), followed by an understanding on selection of suitable analytical technique, risk assessment of variables, method development using DoE, validation process for model and control strategy. At the final stage, AQbD focuses on life cycle management which included control strategy and continual improvement.

IMPORTANT COMPONENTS OF AQbD

Moving a step forward, to have a better understanding of AQbD, the following paragraphs describe the vital components of AQbD and their role in the product life cycle.

(1) ANALYTICAL TARGET PROFILE (ATP)

A fundamental component of AQbD is having a pre-defined objective that stipulates the performance requirements for the analytical procedure.

These requirements are derived from the Analytical Target profile (ATP) like given as below -

Assay: The procedure must be able to quantify [analyte] in presence of [X,Y,Z] over a range of A% to B% of the nominal concentration with an accuracy and uncertainty so that the reportable results fall within +-C% of the true value with at least 90% probability determined with 95% confidence. For example –"The assay procedure must be able to accurately and precisely quantify drug substances in film coated tablets over the range of 70% - 130% of the nominal concentration with accuracy and precision such that reported measurements fall within +_3% of the true value with at least 95% probability". Consider the result of a potency assay of 98.0% label claim for a lot to be release against a lower specification of 95.0% label claim. If the potency method has been verified to adhere to the above ATP statement, the risk that the true lot potency is out of specification (<95.0% label claim) is less than 5%. That is, the potency method provides a result that ensures the true assay value is +_3% of the reported value (95.0% to 101.0%) with at least 95% probability, or there exists less than 5% ([1-0.95]*100) chance that the true assay value is 101.0%.

Impurity: The procedure must be able to quantify [impurity] relative to [drug] in the presence of components that are likely to be present in the sample within the range from the reporting threshold to the specification limit. The accuracy and precision of the procedure must be such that the reportable results falls within +_ D% of the rue value of the impurity levels from 0.05%to 0.15%wih 80% probability with 95% confidence and within +_E% of the true value for impurity levels > 0.15% with 90% probability determined with 95% confidence.

The concept of ATP parallels the concept of Quality Target Product Profile (QTPP) described and defined in ICH Q8. The ATP defines the requirement for the "product" of the test procedure, which in this case is the reportable result. Criteria defined in the ATP refer to the quality data attributes of the reportable results ie accuracy, and measurement of uncertainty, which includes all the sources of variability including precision. ATP defines the objective of the test and quality requirements including the level of confidence, for the reportable results that allows the correct conclusion to be drawn regarding the attributes of the material that is being measured. The ATP serves as a reference point for assessing the fitness of an analytical procedure not only in the development phase but also during all the changes within the analytical lifecycle and is not linked to a specific analytical procedure. It is conceivable that more than one analytical method can meet the requirement of an ATP. USP general chapters <233> and <10>

Existing procedures also can be evaluated in terms of their ability to meet an ATP. When using a compendia procedure for the first time, an ATP can be derived from the monograph specifications, a performance based monograph, and any existing knowledge of the product.

In assessing new or existing procedures for their capability to meet an ATP, analysts can use statistical methods for analyzing prospectively designed studies. In case of existing procedure for which significant historical data are available such as stability studies, laboratory investigations etc, it can trigger additional studies that aim to understand and reduce or eliminate sources of variability and improve data quality to meet ATP

(2) RISK MANAGEMENT

A high degree of confidence is needed that the analytical method will generate reportable results that meet the ATP requirements under all conditions of use as the method progress through the lifecycle. Quality Risk Management (QRM) for analytical procedures can be dined as a systematic process for the assessment, control, communication and review of risks to the quality of data across the product lifecycle. Process mapping tools and Ishakawa diagrams can be employed to ensure a rigorous approach is used to reach and identify all potential variables that may affect data quality. Like sampling, sample preparation, standards, reagents, facility and equipment operating conditions. The identified variable then should be evaluated using appropriate risk-assessment tools and prioritized experimentation to understand, eliminate or mitigate areas of risk. An approach known as CNX (Control, Noise and Experimental) can help classify all identified variables. A decision can be made concerning which variables should be controlled (C), which are potential noise factors (N) and

which should be examined experimentally (X) to determine acceptable ranges. As part of this exercise, analyst should provide and document justifications (prior knowledge, scientific rationale or others) for the assignments made. Risk analysis tools can then be used to screen experimental (X) variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies then provide justification of the critical variables and their acceptable ranges (from the risk assessment and experimental work) are inputs in the Analytical control strategy and are explicitly specified in the analytical procedure.

(3) ANALYTICAL CONTROL STRATEGY

The analytical control strategy plays a key role in ensuring that the ATP is realized throughout the product lifecycle as part of developmental, continual improvement and change management. The controls can include variables and aspects related to the sample, sample preparation, standards, reagents, facility and equipment operating conditions. Historical experience, the forma of value reported (eg number of replicates) and frequency of monitoring and control. A scientific risk based approach can be applied to the assessment of a control strategy's suitability across different sites and quality risk management tools should be used to guide these activities as a risk mitigation plan.

(4) KNOWLEDGE MANAGEMENT IN AQbD

Knowledge management can be defined as a systematic approach to acquiring, analyzing, storing and disseminating information related to products, manufacturing processes and components. Knowledge management should include but is not limited to development activities, technology transfer activities to internal sites and contract laboratories, validation studies over the life cycle of the analytical procedure and change management activities. The knowledge gathered to develop the method understanding should be collected in a repository and shared as needed to support implementation of the control strategy across sites that use the analytical procedure.

In order to provide a holistic approach to controlling an analytical procedure throughout its lifecycle, a three stage concept can be proposed that is aligned with current validation terminology –

Stage-1: Procedure design (development and understanding)

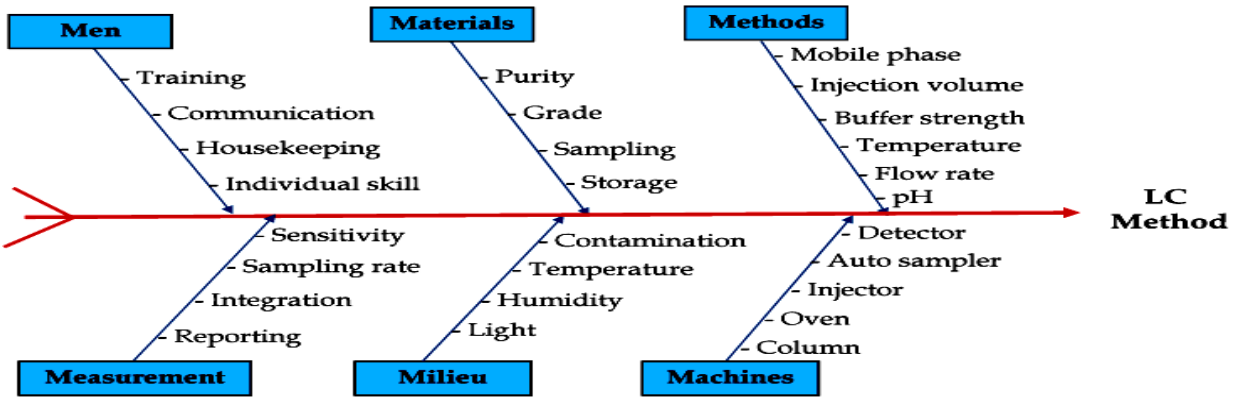
Stage-2: Procedure Performance Qualification

Stage-3: Continued Procedure Performance verification

Stage-1: Procedure design

Once the ATP is established and the requirements for data quality (accuracy and uncertainty) of the reportable results are defined, it is the responsibility of the of the analyst to select an appropriate technology and analytical procedure likely to meet the requirements of ATP

The next step would be to gain an understanding on how these potential sources of variability in the proposed analytical procedure affect the performance characteristics. Tools such as process maps and Ishikawa diagrams (fishbone) can be used to provide structure to a brainstorming and information gathering exercise. A simplified example of fishbone / Ishikawa diagram for purity LC method is as depicted as below -



Risk assessment tools (ICH Q9) then can be used to identify potential variables in the procedures that may need to be controlled to ensure optimum performance and to prioritize experimentations to eliminate or mitigate areas of risk. CNX can help to classify all the variables.

Based on historical knowledge and an assessment of risk, analyst can make and documents decisions about which variable will be classified as C and N and which variables will be classified as X and needs to be investigated experimentally via DOE. Eg. Of C variables – detector or column type or system to be used. Eg of N variables – environmental and routine operating conditions. Eg of X variables – temperature, flow rate, pH

Techniques like comparison matrix (CM), Risk Estimation Matrix (REM), Preliminary Hazard Analysis (PHA) and Failure Mode Effect Analysis (FMEA) are commonly used for risk assessment studies and screening can be accomplished through low resolution experimental designs like Fractional Factorial design, Taguchi design and Plackett-Burman design.

Stage-2 – Procedure Performance Qualification

The objective of this stage is to demonstrate that the procedure is fit for purpose. This stage confirms the analytical procedure is capable of delivering reproducible data that consistently meet the performance criteria defined in the ATP while operated subject to the noise variables that may be experienced. Procedure performance qualification is carried out either to qualify a new procedure or to revise the conditions or operating environment of an established procedure. The analytical procedure used in the study should be based on available knowledge and understanding. The analytical control strategy will be refined and updated as a consequence of any learning from the study. For eg : Further controls can be added to eliminate sources of variability that are identified during the routine operation in the analytical laboratory or replication levels (multiple preparations, multiple injections) to reduce the overall uncertainty in the results reported.

When analysts believe that there may be a risk of variation in the procure performance, additional checks may be included to detect unacceptable levels of variations in the procedural performance. For eg. If there is a risk in the variation of peak separation between critical pairs in reducing resolution injection due to column packing batch to batch variation, a check may be included to ensure that the peak resolution is sufficient to meet the ATP requirements.

Stage – 3 - Continued Procedure Performance verification

The purpose of this stage is to provide ongoing assurance that the analytical procedure remains in a state of control throughout its lifecycle. This stage includes both routine monitoring of the analytical procedure's performance and evaluation to determine if the analytical procedure as a result of any change is still fit for purpose. A system or systems for detecting unplanned departures from the analytical control strategy is essential to accomplish his goal.

(5) DESIGN OF EXPERIMENT (DoE)

In accordance with the requirement of ICH Q8 guidelines, regarding "design space" in product development, method operable design region (MODR) can also be established in method devel-

opment stage which can serve as a source for robust and cost effective method. MODR is the operating range for the critical method input variable (similar to CQA) that produces results which consistently meet the goals set out in the ATP. MODR permits the flexibility in various input method parameters to provide the expected method performance criteria and method response with resubmission to FDA. The implementation of DoE in method development phase requires a huge understanding in selection of input variables and output response. DoE in AQbD approach includes the following –

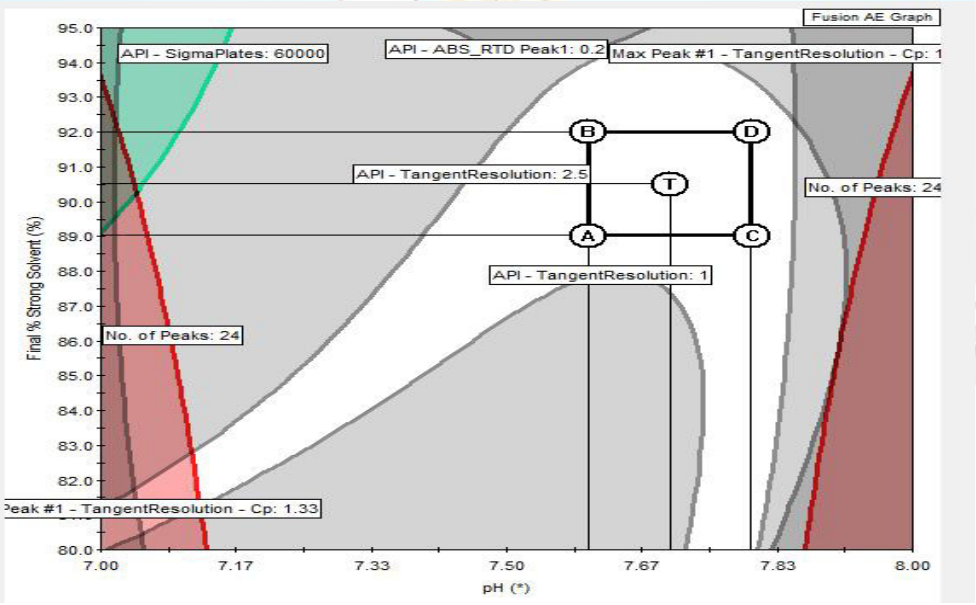
(i) Screening – this stage identifies the various critical method parameters to be considered for the optimization experiments.

(ii) Optimization – Here, quantitative measures from CMP either from screening or directly from risk assessment can be incorporated. This would then transform to a base for scientific understanding of the relation between the input variables (CMP) and output response which will show their effect on method performance and ATP.

(iii) Selection of DoE tools – 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 results and variable. For eg. If effect of all input variables and their interactions are to be measured, factorial design can be applied which can then be considered and optimized with RSM (response surface methodology) Taguchi method can be used with lower number of experimental runs when compared to factorial designs but the interactions confounded need to be resolved. Where large numbers of input variables are to be studied without interaction effects, Placket-Burman methods can be used.

(iv) Surface plots – A model contour plot (2D plot) for MODR is as shown below. The plot shows the impact of pH (x-axis) and % aqueous phase (y-axis) on retention time of analyte while factors like flow rate and other instruments configurations are controlled. All runs are performed and the influence of the factors are analyzed and evaluated by various software such as Minitab, SAS, SPSS or even Microsoft Excel, Fusion AE, Design Expert etc

(v) Model validation – Prior to choice from contour graph, the predicted values from the targeted method response has to be validated by actual experimental run. Then the regression analysis has to be carried out to validate the model statistically.



PAT and AQbD:

For the effective implementation of process analytical technology (PAT) system, parallel development of analytical QbD is highly recommended. PAT is based on two major components: (a) understand-

ing of the scientific and engineering principles involved manufacturing process; (b) identification of the variables which affect product quality. According to the FDA draft guidance, "the desired state of pharmaceutical manufacturing is that product quality and performance are ensured through the design of effective and efficient manufacturing processes" in which continuous and real time quality assurance was recommended. Once the properties of the drug product components are understood, the processing variables that control the relevant properties must be identified. Identification of these variables necessarily requires a multivariate approach. Now, pharmaceutical industries are in progress of establishing specific process understanding and design process analytical control strategies to make PAT approach more effective tool

HOW TO IMPLEMENT AQbD IN CURRENT REGULATORY SCENARIO:

In future, analytical QbD has to be introduced in the method development phase and has to be validated for the method performance along with the validation protocol. For a given generic drug product development, to implement analytical QbD, the following may be considered.

(i) Construct a QTPP (a profile based on the product specification as outlined in the FDA approval).

(ii) Analyze each product specification for criticality.

(iii) Assess and justify the analytical method development and suitability to support the criticality.

(iv) Select the suitable analytical technique to meet the ATP and then QTPP.

(v) Perform risk assessment for the selected method

(vi) Identify the quantitative and qualitative variable that affects the method performance and method responses to be measured

(vii) Use suitable DoE experiment to optimize variable and establish scientific understanding.

(viii) Find the region, models to assess the robust and economic operation for the method variable.

(ix) Validate the models and MODR region using experimental verification at different points to prove robustness

(x) Then validate the method in the operable region for the method performance and subject to control strategy and improvement.

It will be easier for the regulatory agencies to evaluate and understand the AQbD with the described scientific and logical development data and give the approval for the product on the basis of the scientific work carried out within the AQbD domain.

Challenges for AQbD and its application in present scenario:

(i) Being relatively newer to the world of analytical sciences, AQbD poses some challenges for its implementation, especially when this not exactly a regulatory requirement currently but would very soon become one in the near future.

(ii) First of all, it may need a paradigm shift from submission of traditional information rich documents to scientifically sound, knowledge rich documents wherein there is no regulatory expectations of technology transfer and method re-validation.

(iii) Very clear and concise definitions of MODR, control strategy, CMA and method performance criteria are required to be established since multiple terminologies are in use across the globe in regards to AQbD.

(iv) Training and education of resources in industry and regulatory agencies is another challenge for the effective implementation of QbD concepts in the analytical space.

(v) Also, there is a dire need to have clear defined guidelines regarding documentation of knowledge generated during method development so that it can then be used for regulatory submissions.

EXAMPLE FOR APPLICATION OF AQbD PRINCIPLES TO STABILITY INDICATING METHOD DEVELOPMENT

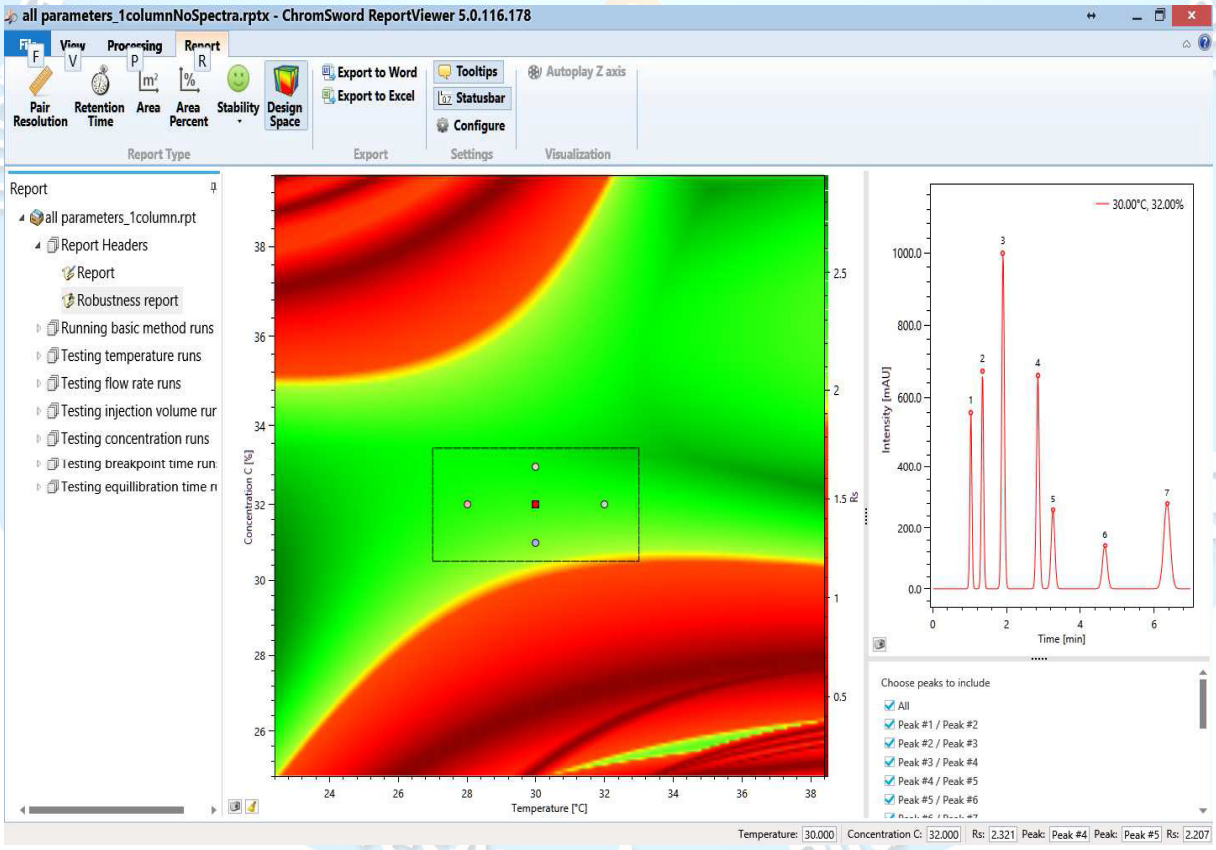
In the following paragraphs, AQbD principles are applied to stability indicating method develop-

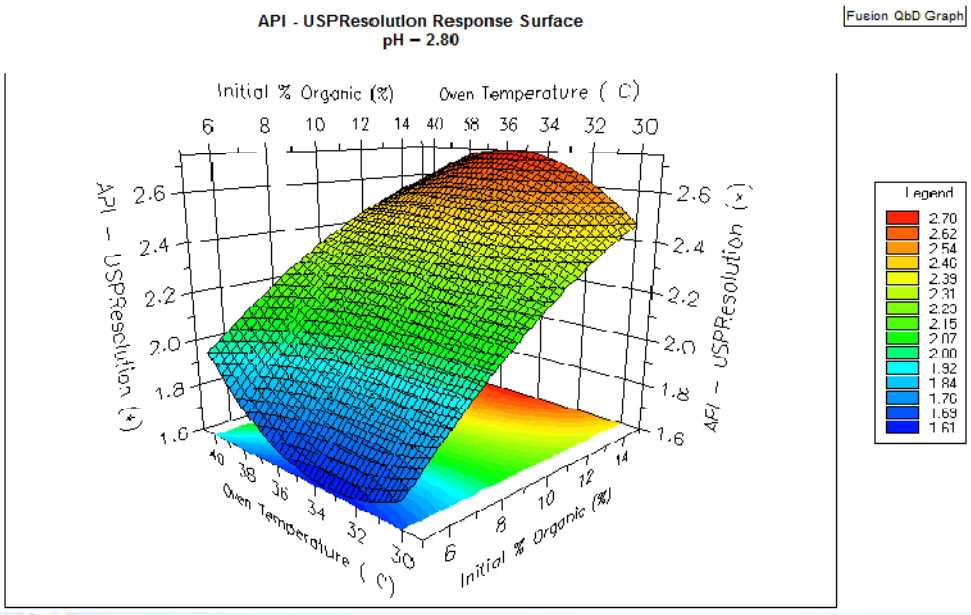
ment for Linagliptin on Agilent 1200 Infinity series Method development system. Fusion AE software runs the instrument unaided, sets up the design of experiments, tracks components and models the responses. A statistical DoE concept was applied to screen the mobile phase and column chemistry and for method optimization experiments. Multivariate analysis of CMPs such as mobile phase composition, pH and column temperature was used to determine the final design space.

After the QTMP is set, the next stage involves initial chemistry screening based on prior knowledge and early risk assessment with mobile phase type, pH, column chemistry and run time as the variables. The chosen elution mechanism was a gradient based on the QTMP. A statistical design of experiments utilizing full factorial design or other default design can be used.

After peak integrations, the data is exported to Fusion AE software, which is used to model the data. The CMAs, including number of peaks, resolution and peak having tailing less than 1.2, are optimized and the software models the contour plot for various columns. The contour plot of the of the modeled data for Zorbax Eclipse Plus C8 (below) shows the shaded region as the acceptable region where all the CMAs are met.

The surface plot (further below) shows the region where gradient time greater than 8min and pH greater than 5.5 leads to the maximum number of integrated peaks. This method, in general, was found to be sensitive to pH and gradient time/slope within a range hereby indicating a stringent control on these method parameters.





The next stage involves mean performance optimization with starting/ending gradient percentage/slope, run time, a narrower pH range and temperature as variables. The column chemistry and mobile phase pH are kept constant for determining optimal conditions.

In the final stage, the design space is determined for the CMAs in terms of CMPs. The design space is a region in which changes to method parameters will not significantly affect the results. Operating within the design space leads to a more robust method, as small deviations from the method will not significantly impact the analysis. The design space incorporates both the mean method performance and the method robustness. The unshaded region in the graph defines the design space for the critical responses in terms of the CMPs studied.

QbD method development helps to better understand the variables and define robustness parameters and resolution limits. As a part of QbD implementation, several column chemistries were evaluated in addition to the mobile phase and other method parameters. After conducting validation experiments, a control strategy should be implemented. Over time, continuous improvement can be achieved by expanding the robust region to include more variables.

The automated method development described here not only takes less time compared to manual method development but also brings the advantage of low failure rates during method validation and transfer.

CONCLUSION:

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

The recent focus within the pharmaceutical industry and associated regulatory bodies on QbD approaches to analytical method development are a positive sign that both the industry and regulators are acknowledging the importance of understanding the contribution of measurement uncertainty to drug processes and products.

For the separation science community, the recognition that multifactorial (DoE) approaches for chromatographic method development (and verification) provide a scientifically sound strategy for generating robustness and ruggedness understanding is also welcome especially as the community has been developing methods in such a way for some time now. It is probably notable that as this topic gains momentum, it is envisaged that software developers who have been developing in silico tools to help separation scientists achieve more efficient method development will have an increasing demand upon them to assist he industry in being able o describe MODR's for the ATP.

Furthermore, being able to perform such experimental designs in an automated way will be extremely important in the adoption of his approach. The application of QbD principles to analytical method development and validation will probably result in a move from the fixed method validation criteria defined in ICH Q2, towards criteria designed for specific requirements. Just as fixed method validation requirements may become a thing of the past, fixed instrument qualification criteria, such as the one followed in paper protocols, may become obsolete. Instead, the most likely option would be the configurable electronic qualification. The flexibility needs to be fully controlled to satisfy regulatory requirements, while the move from paper based protocols towards electronic qualification also satisfies the data integrity concerns of regulatory agencies.

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