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A Review on Quality by Design Approach for Analytical Method Development

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Abstract

Quality-by-design (QbD) may be a systematic approach to drug development, which begins with predefined objectives, and uses science and risk management approaches to realize product and process understanding and ultimately process control? The concept of QbDare often 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 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 within the article, after which the variables are optimized. The final method is validated and a control strategy is put in place. Additionally, global harmonization of QbD terms and explicit guidelines on implementation of the QbD approach in all fields of product development including Analytical Techniques is necessary to streamline the path towards embracing this unique and effective approach.

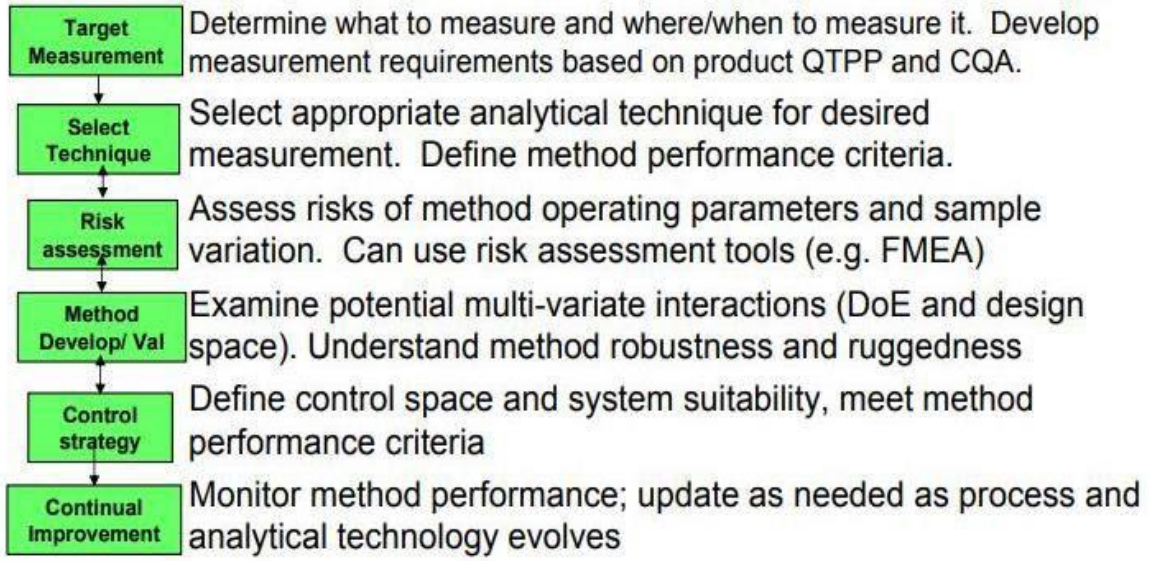
Keywords*: - Quality, Quality by Design, Analytical QbD, Method Operable Design Region (MODR.*

INTRODUCTION

Quality-by-design (Qbd) has become an important paradigm in the pharmaceutical industry it was introduce by the US Food and Drug Administration. Quality is one among the elemental criteria additionally

to safety and efficacy for any entity to be qualified and approved as a drug. For ensuring Consistency of performance of pharmaceutical products and systems, the recent emphasis has been on building the "quality" instead of merely testing it. This philosophy forms the idea of Quality intentionally (Qbd). ICH guidance Q8 (R2) describes QbD as, "a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" As per Janet Woodcock (2004), "Means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches."QbD is all about designing an appropriate process and understanding process performance for the specified product performance. Major element within the overall scheme is continuous improvement, which successively is predicated on the knowledge gained during process understanding. The concept gravitates towards a 'desired state' marked with 'regulatory flexibility' focusing on scientific knowledge building, superior design, demonstration of performance, Quality Risk Assessment (QRM), Design of Experiments (DoE), Process Analytical Technology (PAT) tools, continuous improvement and learning, and life-cycle management.

QbD APPROACH FOR ANALYTICAL METHODS [2]



Benefits of Analytical QbD [1]

- Increased understanding and control
- Beyond traditional ICH procedure of method validation
- Flexibility in analysis of API, impurities in dosage forms, stability samples, and metabolites in biological samples
- Reduction in variability in analytical attributes for improving the tactic robustness
- To stay the values of analytical attributes within the Pharmacopoeial monographs, and faraway from Out Of Specification (OOS) limits
- Smooth process of method transfer to the production level
- No requirement of re-validation within MODR

Lifecycle of Analytical Method Developed by Quality by Design (QbD) Approach [5]

The development of the drug molecules brought a revolution in human health care. The process of drug development starts with the innovation of a drug molecule that has showed therapeutic value to battle, control, check or cure diseases. Development of drug products starts from screening of several thousands of molecules and screen out all of them except the target drug substance through its benefit to different diseases, toxicological evaluation, pre-clinical and clinical evaluation and finally detail review by regulatory bodies like United States Food and Drug Administration (US FDA), European Medicines Evaluation Agency (EMEA) etc.

Pharmaceutical dosage forms are generally considered as safe, effective and have intended quality when its drug substances (i.e. active pharmaceuticals ingredients) are of appropriate, does not pose toxicological effect, manufactured according to validated methodology following current Good Manufacturing Practice (cGMP), evaluated for its physiochemical, microbiological properties with appropriately validated methodology, has required bioavailability and it is used for the target disease at appropriate does. Hence it is likely that the quality of drug products for its different dosage form may vary in company to company. A branded/innovator drug product is initially discovered and developed by a pharmaceutical company.

Innovator of branded drug got approval from regulatory bodies to initiate marketing and for which regulatory bodies review innovator drugs labeling, administrative, animal, clinical,

bioavailability, toxicological, chemistry, manufacturing and control documents along with inspection of the manufacturing, packaging and testing site to ensure that drugs are safe and effective. Once innovator got approval for the branded product, they can exclusively market and sell this 'brand-name' product as long as the company has got exclusivity and patent protection. Quality of product has been assessed through its physiochemical and microbiological properties. Product specification represents its quality requirements and analytical methods play vital role to understand level of compliance for different physiochemical and microbiological profile specified in product specification of drugs products from the stages of development to marketing and post marketing. Selection of appropriate methods is thus important to ensure quality product and to ensure safety, efficacy and stability of drug product. Appropriately standardized analytical methods and specifications for raw materials (API and Excipients) and finished products of generic products are generally available in Pharmacopeial monographs. Currently there are different Pharmacopoeial bodies available in the world such as United State Pharmacopeia and National Formulary (USP/NF), European Pharmacopoeia (EP), Japanese Pharmacopoeia (JP), and British Pharmacopoeia (BP) etc. who has published their volume generally in every year. All of the compendia monograph/standards are generally proposed by sponsors which are reviewed by an expert group called Pharmaceutical Forum and make available for public opinion before it is considered as official by Pharmacopoeia by its expert committee.

Generally sponsor of Pharmacopoeial methods are innovator of drug or generic manufacturer throughout world. However, until the patent period methods are generally not disclosed by innovator. Pharamacopoeial methods are considered as complete based on validation documents of sponsor and Pharmacopoeial body and have appropriately validated. However, it is recommended by USP to perform a verification during its first use to verify their suitability in actual usage condition i.e. change of personnel, equipment and reagents.

In the Federal regulation of United States, this requirement has been established in 21 CFR 211.194(a)(2) of the cGMP regulations, which states that the “suitability of all testing methods used shall be verified under actual conditions of

use." There are still many pharmaceutical drugs within the market which are yet to incorporate within the pharmacopoeia, called non-pharmacopeial molecules that lack appropriate methods for analysis to assess their quality. But lot of such products are already launched in Bangladesh as country is allowed to be out of patent law as of the agreement of World Trade Organization (WTO) and can produce any product irrespective of patent period until year 2033 (Tania Sultana, et.al., 2017).

Taking advantages of this every year a significant number of new products are launched in Bangladesh by different local companies those are still within Patent and Exclusivity period. Testing methodology of those are yet to publish in Pharmacopoeia and hence appropriate method to evaluate quality of these drugs are very important to ensure its quality. A good analytical method should have following features as shown in **Table 1**, which allow its efficiency and superiority to use in regular quality control testing.

When selecting/developing a method it has carefully assessed in a structured manner for risks, and are challenged to determine if robustness and ruggedness criteria are satisfied to understood method performance and need of any further improvement. It is essential for analytical method and technology to produce precise, accurate and reproducible data regardless of the study approach. Therefore, analytical methods, which are the measure of quality of the drugs, play a very comprehensive role in drug development and follow up activities.

Table 1: Requirement of good analytical method

Sr. No.	Parameters	Characteristics
1.	Analytical Scientist	➢ Develop within shortest possible time ➢ Utilize knowledge based on Sciences ➢ Considering risks focus on critical parameters
2.	Routine Use	➢ Robust, no problem during routine use ➢ Changing people, materials, Environment etc. ➢ No out of specifications due to lack in method
3.	Quality Assurance	➢ Suitable for Quantification
4.	Regulatory Affairs	➢ Enough Documentation for registration
5.	Finance	➢ Lowest development and validation Cost

They assure the standard, stability and reliability of a drug product (Raman et al. 2015). A traditional approach to method development always involved the time-consuming Process of varying one system parameter at a time, examining its effect on the method, and system operation. This generally requires an outsized number of experimental runs and in most situations the developed method requires further development. Moreover, developed method could fail to meet desired separation during validation, method transfer, or out of specification studies. The global pharmaceutical industry has skilled substantial changes within the previous couple of decades. In 21st century pharmaceutical firms face major challenges to ensure patient safety by improving product quality due to regulatory stipulate. The announcement by US FDA "Pharmaceutical CGMPs for the 21st Century-A Risk Based Approach" was intended to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. The regulatory bodies are encouraging the early adoption of new technological advances by implementing various scientific tools such as PAT (Process Analytical Tool) and QbD (Quality by Design). The significant number of reports on out-of-trend (OOT) results, Out Of specification (OOS) results due to deficient analytical method of pharmaceutical analysis indicating that the present system of pharmaceutical industry is not immune to these issues. Moreover, a significant number of QC related warning letters issued by US FDA and EMEA demonstrated that companies have problems with risk management system in analytical methods and related systems. Hence, pharmaceutical industries are striving for new strategy and/or new element which can be add/replace traditional method development approach. At this juncture, implementation of QbD has been made mandatory in some countries, especially by EMA (Europe Medicines Agency), US FDA and other ICH countries. International conference on hominization (ICH) Q8 (R1) guideline defines QbD as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, supported sound science and quality risk management". Quality assurance personnel in Pharmaceutical Industries are now believes that AQbD will be a better solution to avoid OOT and OOS and to reduce risk in method failure. QbD approach to method development can potentially cause a more robust/rugged method thanks to the stress on risk

management. In QbD approach, the impact and interactions between critical method variables are understood employing a Design of Experiments (DOE) approach, which includes statistical multi-variate analysis and modeling. The allowed deviations of the method variables are determined within the design space-Method Operable Design Region (MODR). QbD concept can be applied to analytical method development, because of possibility to evaluate many variables that significantly affect the method performance. These variables are such as instrument settings, sample characteristics, method parameters etc. Especially for a chromatographic separation are the variability due to HPLC instrument configuration, column selection, flow rate, injection volumes, pH of buffer, column temperature, and % ration of mobile phase etc.). These are test parameters influence the robust behavior of the method. A design of experiments (DOE) approach is adopted to define the MODR for these variables are thus important. A simple step by step AQbD philosophy for development of a comprehensive science and risk based simple, rapid and sensitive HPLC method for the analysis of a Drug product in Pharmaceutical Quality system is presented in **Table 2**.

Table 2: Steps in Analytical Method Development by QbD approach

Step	Activities	Data to generate
Step 1	Selection of Analytical Method Target Profile	➢ Determine Analytical Method Target ➢ Profile Qualitatively by Using Fish Bone Diagram ➢ Method Parameters/Factors/Variables (e.g. Mobile Phase, Column, pH of Buffer, Column Temperature, Injection volume, Particle Size of HPLC Column, Analyte type, Diluent type, Detector etc.) ➢ Method Performances/Attributes /Responses (e.g. Accuracy, Precision, Robustness, Retention time (RT), Theoretical plate (N), etc.)
Step 2	Literature Search	➢ Data should be collected for the intended analyte through literature survey ➢ Molecular structure and molecular weight ➢ pKa ➢ to understand whether the molecule is acidic, basic or neutral ➢ Type of functional group - Presence of Chromophore ➢ Log P (partition coefficient) - Solubility

		- Available Method
Step 3	Identify method parameters by method scouting	➢ Define method parameters based on: - Analyte physiochemical Properties - Physiochemical Properties of Mobile Phase - Stationary phase compatibility with Analyte and Mobile Phase
Step 4	Identify predictive critical method parameters by Qualitatively/Quantitatively	➢ Qualitative Method: Discard predictive values like column length, Injection volume o Include unpredictable items like pH of buffer, mobile phase composition, Flow Rate - Quantitative Method o Risk Assessment for high risk items which may have high impact on response e.g. pH of buffer, mobile phase composition, Flow Rate
Step 5	DoE for Multivariate Interaction Study	➢ Set up Critical Method parameters to the responses over a range
Step 6	Screening and Optimization	➢ Scientific understanding of relation between quantities of input variables (CMP) and output response which will show considerable effect on method performance (Interaction plot, surface plot, Contour plot etc.) ➢ Define method operable design space
Step 7	Define Final operable Method and Execute Method Validation	➢ Stability indicating ➢ study specificity (force degradation), Accuracy, Precision, Robustness, Solution Stability etc
Step 8	Monitoring and Lifecycle Management	➢ Evaluate Market products and RLD

Analysis of Pharmaceutical products includes a wide range of simple and instrumental analytical methods, but the most widely most used analytical methods for quality assurance are spectroscopy and chromatography based. Most quantitative analysis requires measuring specified components in the presence of sample matrix and /or related substances, therefore isolation or separation of the components are required preceding quantitative analysis. In such cases chromatographic techniques are used for quantitative analysis.

In cases where matrix interference is not observed quantitative measurements are made using spectroscopic or titration methods directly. HPLC has become the most important separation technique for analyzing drug substance and drug product. In today's laboratory, testing is for the foremost part conducted by HPLC, and most wet chemistry methods became obsolete.

Tools of QBD [3]

Design of Experiments In accordance with the requirement of ICHQ8 guidelines,

regarding "design space" in product development, method operable design region (MODR) can also be established in method development phase, which could function a source for robust and price effective method. MODR is that the operating range for the critical method input variable (similar to CQAs) that produces results which consistently meet the goals began within the ATP. MODR permits the pliability in various input method parameters to supply the expected method performance criteria and method response without resubmission to FDA. It is based on a science, risk based and multivariate approach to evaluate effects of various factors on method performance. FDA has suggested conducting MODR alongside method validation as most recommended. Once this is often defined, appropriate method controls are often put in situ and method validation are often administered. There are many analytical works which are reported using experimental design supported factorial or fractional factorial design or response surface methodology. But those works were limited to the development of mathematical models to correlate input variables (Xn) and output responses variables and output response. DoE in AQbD approach includes the following.

a) Screening In screening, qualitative input variables can be screened out. It identifies the varied critical method parameters (CMP) to be considered within 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.

b) 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.

c) 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 amount 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 are often applied then it are often 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 are often used. A typical selection of techniques is shown in Table 4.

Table 4: Selection of DOE tools in analytical quality by design.

Design	Number of variables and usage.	Advantage	Disadvantage
Full factorial design	Optimization/ 2-5 variables	Identifying the main and interaction effect without any confounding	Experimental runs increase with increase in number of variables
Fractional factorial design or Taguchi methods	Optimization/ and screening variables	Requiring lower number of experimental runs	Resolving cofounding effects of interactions is a difficult job
Plackett-Burman Method	Screening or identifying vital few factors from large number of variables	Requiring very few runs for large number of variables	It does not reveal interaction effect
Pseudo- Monte Carlo sampling (pseudorandom sampling) method	Quantitative risk analysis/ optimization	Behavior and changes to the model can be investigated with great ease and speed. This is preferred where exact calculation is possible	For nonconvex design spaces, this method of sampling can be more difficult to employ. Random numbers that can be produced from a random number generating alogrithm
Full factorial Design	Optimization/ 2-5 Variable	Identifying the main and interaction effect without any confounding	Experimental runs increase with increase in number of variables

d) Method Operable Design Region (MODR) and Surface Plots:

A model contour plot (2D plot) for MODR concept is shown in Figure 1(a). The contour plot may be a 2D response plot representing the impact of pH (xaxis) and a couple of aqueous phase (y-axis) on retention time of analyte, whilst factors like flow and other instrument configurations are controlled. Numbers like −1, −2, +1, and +2 in both axes represent the coded level of variables utilized in DOE plan. This contour is suitable for the response if it's nonlinear and therefore the relationship between input variable and method response has more curvature effect. Then MODR are often selected from contours using mathematic models. The anticipated value of method response are often verified by using actual experimental run as a neighborhood of model validation. There's another surface model which will be obtained by means of simulation that gives the change of response with reference to variables, which is more suitable for linear relationship Figure 1(b).

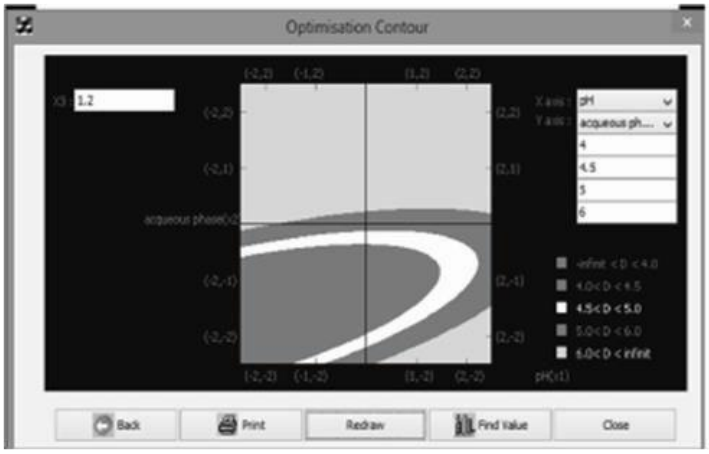


Figure 1(a)

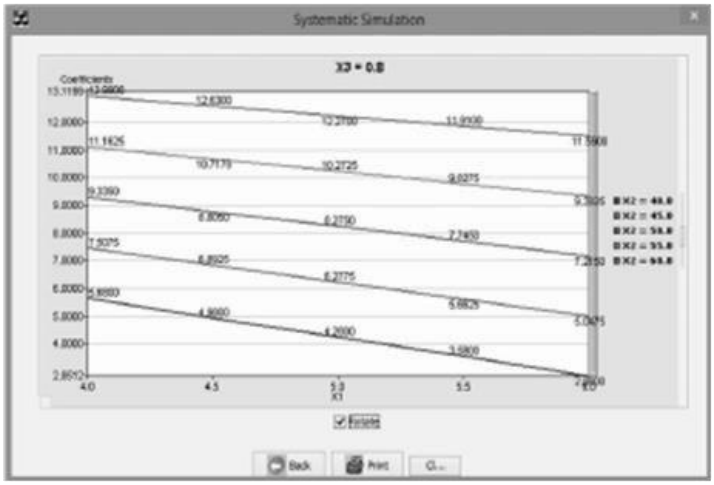


Figure 1(b)

QbD Principles for Analytical Method Development [6]

To ensure the standard product analytical method should even be in unison with the QbD and PAT. Thus, due stress should even be laid on regulatory guidelines for AQbD describing the event of method as per DoE including risk management and details of quality systems required.

Proposed key definitions for AQbD [6]

According to ICH Q8, main terminologies utilized in the method optimization are Quality Target Product Profile (QTTP), Design Space (DS) and style of Experiments (DoE). The analogous terminologies for analytical method development employed by quality experts are Analytical Target Profile (ATP), Method Operable Design Region (MODR) and Method Development Strategy (MDS).

Key definitions for AQbD [1][6]

Mostly the QbD technique is applied to the broad arena of development. This necessitates a discussion of application of Qbd to analytical techniques. The time has come to form the normal analytical method obsolete and embrace the info driven and scientific approach of AQbD. The key concepts and activities related to successful implementation of AQbD are discussed below during a step-wise manner.

1. Creation of data Space

The generation of data space constitutes elementary ground work essential for designing quality into a product or the tactic. For the later, it starts with defining aim of the tactic and its applicability under various situations. Once this is often known efforts to build-up knowledge space involve broad understanding 3C's, i.e., contribution, correlation and consequences. Contributors mainly include, but are limited to 'material attributes' and 'method parameters'. Contributors are often system attributes, risk assessment tools, and experimental design, etc., which could affect the results. Correlation among contributors and consequences most vital during risk assessment and data analysis. During data analysis, it directs for adequate selection of design model and representation of knowledge, etc. Consequences are the consequences of contributors on the system, method and quality attributes. With understanding of those, knowledge space is further strengthened as method development reaches to an end and therefore the same is beneficial for deciding the control strategy and life cycle management

KNOWLEDGE SPACE [1][6]

Activities involved in the building knowledge space

2. Analytical Target Profile

In AQbD, Analytical Target Profile (ATP) is similar to Quality Target Product Profile (QTPP) element in QbD. ATP is much for method development or it's simply a tool for method development and has been mentioned within the ICH Q8 R(2) guidelines. It describes the tactic requirements which are expected to be measured. Recently PhRM5A and EFPIA defined ATP as: "ATP may be a statement that defines the method's purpose which is employed to drive method selection, design, and development activities."[1] Another definition of ATP as given by USP council of experts in their stimuli article is, "the requirements for the "product" of the test procedure, which during this case is that the reportable result" or "the objective of the test and quality requirements, including the expected level of confidence, for the reportable result that permits the right conclusion to be drawn regarding the attributes of the material that is being measured" It is basically, the combination of all performance criteria required for the intended analytical application that direct the method development process. An ATP would be developed for every of the attributes defined within the control strategy. The ATP defines what the method has to measure (i.e., acceptance criteria) and to what level the measurement is required (i.e., performance level characteristics, such as precision, accuracy, working range, sensitivity, and the associated performance criterion). The ATP requirements are general ones and accompany primarily to the intended purpose, to not a selected method. Any method conforming to the ATP is taken into account suitable, thus giving the method regulatory flexibility. The ATP are often considered the focus for all stages of the analytical life cycle.

Applying QbD principles to analytical methods committed an organization to incorporate the best scientific practice by linking prior knowledge of techniques and methods to an ATP, a mechanistic understanding based on chemical and physical knowledge of the factors that influence method performance, an investigation of multivariate relationships across method factors and an understanding of how variation in these method factors affects the analytical result. This knowledge provides an insight into the contribution that variability within the method makes to the general product and process variability, ensures a more focused

method control strategy and provides a radical understanding of the impact of planned method changes, all leading to better methods in both their operation and outcome.

For the longer term, the ATP concept could also be a way of proposing more advanced regulatory approaches to method submission and review. The ATP is defined with the assistance of data and scientific understanding of the analytical process, which is where the role of data space comes in.

3. Establishment of Analytical Target Profile (ATP)

The foundation of any analytical method developed through QbD principles is 'ATP', which is similar to Quality Target Product Profile (QTPP), as defined in ICH Q8 (R2). USP council of experts define ATP in their stimuli article as, "the requirements for the "product" of the test procedure, which in this case is the reportable result" or "the objective of the test and quality requirements, including the expected level of confidence, for the reportable result that permits the right conclusion to be drawn regarding the attributes of the material that is being measured". ATP is not limited to method development only, but should also bemet during method transfer and also during lifecycle management. Also, ATP is not always limited to single method and more than one method/analytical technique can satisfy the same ATP. Moreover, one can always evaluate available methods to meet ATP. In case of compendia methods, monograph specifications and available performance understanding of the merchandise are often wont to establish the ATP. ATP may be a key parameter in AQbD that facilitates greater continuous improvement of analytical methods and their choice, once the regulatory authorities approve the ATP statement. In pharmaceutical industry, internal change control management system is liable for effective implementation of ATP to supply regulatory flexibility.

4. Identification of potential and critical method variables and attributes

According to ICH Q9, risk assessment are often wiped out three steps, viz., risk identification, risk analysis and risk evaluation. Risk identification involves uncovering of all the Potential Method Variables (PMVs) and Potential Method Attributes (PMAs) including all aspects associated with man, material, machine, method, environment and measurement. This can be through with the assistance of flowcharts and check lists, etc.

Subsequently, PMV sare categorized consistent with their source of origin (by using fish bone diagram) or control required on these (by CNX approach). A simplified example of fishbone/Ishikawa or cause-effect diagram for purity/impurity LC method is depicted in

5. Design-guided method development

Application of DoE principles facilitates understanding of multiple method parameters and variables that tend to affect CMAs, while unravelling the prevalence of (any) interactions and reducing intricacies.

For the successful execution of DoE study, the knowledge of response variables or CMAs, CMVs, their ranges, and best fitting of the mathematical model (s) is obligatory. DoE-based Response Surface Methodology (RSM) is useful in systematic development of analytical methods involving significant nonlinearity.

CONCLUSION

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. Method transfer in QbD is feasible for analytical methods and will enable better, more efficient and continuous improvements for future methods.

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