QUALITY BY DESIGN APPROACH FOR ANALYTICAL METHOD DEVELOPMENT

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ABSTRACT
An application of the Quality by Design (QbD) approach, is to the exemplar of analytical method development, the process commonly referred to as AQbD. The benefits of applying AQbD principle is to identifying and minimizing sources of variability that might lead to poor method robustness and ensuring that the method meets its planned performance requirements throughout the product lifecycle. It allows the analytical method for movement within method operable design region (MODR). The variables which affect the output and subjected to through risk assessment factor are optimized. The final step is to validated and a control strategies. Analytical method developed using AQbD approaches to reduces out-of-trend (OOT) and out-of-specification (OOS) which results into the robustness of the method within the region Continuous improvement is the key to the success of AQbD. Harmonization of QbD terms and specific guidelines on implementation of the QbD approach in all fields of product development is require to design the path towards embracing this unique and effective approach. Owing to the famine of overviews on this topic, this paper endeavor to explicate the AQbD process and also to correlate with product quality by design and pharmaceutical analytical technology(PAT).

KEYWORDS: QbD, AQbD, Analytical, MODR, Quality by Design.

INTRODUCTION
Quality by design (QbD) concept has been introduced in pharmaceutical industry to enhance robust manufacturing process. It facilitate the manufacturing process in term of “six sigma” which is a system of practices developed for systematic improvement of processes to achieve superior pharmaceutical products and ensure patient safety.[1]
ICH consensus vision on Quality is stated as “Develop a harmonized pharmaceutical quality system applicable across the life cycle of the product”. According to ICH Q8 guidance, “quality should be built into the process design rather than testing into the final product”.

The significant number of reports on out-of-trend (OOT) results, out-of-specification (OOS) results, out-of-control (OOC) and out-of-statistical- control (OOSC), indicating that the present system of pharmaceutical industry is need to develop a new analytical method strategy. Hence, pharmaceutical industries are trying to achieve for new strategy which can be replace the existing elements of quality and risk management system. EMA (Europe Medicines Agency) and other International conference on hominization ICH countries, has been made implementation of QbD obligatory. (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, based on sound science and quality risk management”. Definition as per FDA PAT Guidelines, Sept. 2004: A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of new and in-process materials and processes, with the goal of ensuring final product safety.

Recently, United States Pharmacopoeia (USP-NF) and European Pharmacopoeia (EP) updated new chapters in which flexibility is granted for an analytical method that can be changed without the need for revalidation if AQbD approach has been implementation.

A brief literature survey revealed that in the pharmaceutical industry, there is still incomplete understanding of the Analytical QbD process (AQbD).

This paper summerises the implementation AQbD which helps in development of a robust and cost effective analytical method and its correlation with other components of pharmaceutical quality systems. It means the freedom to change method parameters within a method’s design space, referred to as the method operable design region (MODR).

**TRADITIONAL VALIDATION V/S ANALYTICAL QBD**

Now days, analytical method failure is becoming more common during method transfer as well as in quality control departments. It is assumed due to the exception given for robust test compliance by ICH Q2 guidelines. In current practices, chromatographic methods are more commonly employed as right analytics at all the stages during the product life cycle. Common analytical methods for content uniformity, assay, impurity profile, and stability
indicating assay are based on high performance liquid chromatographic (HPLC) or ultra performance liquid chromatographic (UPLC). In connection with chromatography, due to complex parameters involved in the method development phase, low sensitivity, selectivity, and inadequate understanding between method performance and method parameters, always the revalidation protocol has been recommended. On the other hand, in current practice, the implementation of analytical method is based on one factor at a time (OFAT), in which one parameter alone is optimize the method while others remain constant.\[^8\] It failed to provide assurance that the analytical technique is reliable throughout the life cycle of its use. Hence the present strategy of analytical method (i.e., OFAT) development has high risk in method failure and involved lengthy regulatory procedures to introduce any changes in the process which make the process long and costly one. The need for introduction of Quality by Design in Analytical Techniques was felt.

The aim to approaching AQbD is to tackle shortcome of traditional approach. AQbD is based on scientific understanding in method implementation sequences and starts with product quality that relates the risk assessment in method selection and finally a region for high robust and cost effective approach. Different variables are evaluated and duly prioritized. In AQbD, design of experiment is plan in different steps which represents the interaction among the input variables that ultimately affect the method response and results. At this juncture, AQbD paradigm is a recommended strategy to be followed in analytical method development so as to attain regulatory flexibility and reduce OOS, OOT, OOC, and OOSC results, high degree of robustness and cost effective analytical method. Table-1 highlights the differences between the approaches of traditional analytical method validation, Quality by Design for product development and Analytical Quality by design.
Table 1: Comparison between Traditional Analytical method, QbD and AQbD

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Traditional</th>
<th>Product QbD</th>
<th>Analytical QbD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approach</td>
<td>Based on empirical approach.</td>
<td>Based on systematic approach.</td>
<td>Based on systematic approach.</td>
</tr>
<tr>
<td>Specification</td>
<td>Specification are based on batch history.</td>
<td>Specification are based on product performance requirement.</td>
<td>Specification are based on method performance to ATP criteria.</td>
</tr>
<tr>
<td>Quality</td>
<td>Quality Assurance includes end product testing.</td>
<td>Quality is build in the product and process by design and scientific approach.</td>
<td>Quality is developed throughout method development phase and through life cycle management</td>
</tr>
<tr>
<td>Process</td>
<td>Retrospective</td>
<td>Prospective</td>
<td>Prospective</td>
</tr>
<tr>
<td>FDA submission</td>
<td>Only data required</td>
<td>Submission with product knowledge and process understanding</td>
<td>Submission with product knowledge and assuring by analytical target profile</td>
</tr>
<tr>
<td>Cost</td>
<td>Any change to be made in process involve huge cost.</td>
<td>Cost effective. Design is flexible.</td>
<td>Cost effective. MODR is flexible.</td>
</tr>
<tr>
<td>Advantage</td>
<td>Limited and simple</td>
<td>It is extended process Analytical technology (PAT) tool that replaces the need for end product testing</td>
<td>Replaces the need of revalidation</td>
</tr>
<tr>
<td>Target response</td>
<td>Focus on reproducibility, ignoring variation</td>
<td>Focusing on robustness with control variation</td>
<td>Focus on robustness and cost effective method</td>
</tr>
<tr>
<td>Time aspects</td>
<td>One factor optimized at a time.</td>
<td>Several factors are accessed together</td>
<td>Several factors are accessed together</td>
</tr>
<tr>
<td>Variability</td>
<td>Avoided</td>
<td>Understood and explored</td>
<td>Explored and factors contributing to its are optimized</td>
</tr>
</tbody>
</table>
REGULATORY ASPECT OF ANALYTICAL QBD

In year 2002, there was a introduction of ‘Pharmaceutical cGMPs: A Risk-Based Approach’, by USFDA the concept of Quality by Design and continuous improvement were introduced in the pharmaceutical industry. Recently, FDA has approved a few new drug applications based on analytical QbD and alluded the importance and benefits of QbD in analytical method development.[9] Now days, analytical method failure is becoming more common especially during method transfer as well as in quality control departments. It is assumed to be due to the exception given for robustness test compliance by ICH Q2 guidelines. ICH Q10 includes analytical techniques are key part of control strategy. Thus execution of analytical QbD in manufacturing process as control strategy will ensure predetermined performance and product quality. Implementation of AQbD is considered to strengthen the concept of “right analytics at right time” which plays major role in drug product development cycle. 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 in the product quality. There were few conferences, during late 2013 and early 2014, insisting on the implementation of the existing QbD concept to analytical method development.[10] Quality assurance personnel believes that AQbD will be a better solution to avoid OOT and OOS and to reduce risk in method failure. Due to the above cited discussion, analytical method development using QbD approach is a current area of focus and needs to be implemented. The dependence of pharmaceutical development and manufacture on robust analytical data intensifies the need for rigor in analytical method development and increasingly an analytical QbD (AQbD). 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.[6] In fact analytical methods are the indicator of quality of process, product, and robustness throughout the life cycle.

IMPLEMENTATION OF AQbD

The application of QbD concept to analytical method would aid in building quality in the method right from scratch. This technique basically arms us to manage variability and ensures robust analytics. Reliability of an analytical method is demonstrated by its robustness and ruggedness. A processes called as robust if they have the ability to tolerate the expected variability of raw materials, operating conditions, process equipment, environmental
conditions, and human factors.\textsuperscript{[11]} To adopt a suitable design of experiments (DOEs) protocol in AQbD approach to identify a validated MODR for high degree of process-product-analytical method understanding is recommended.\textsuperscript{[9]} Initially, implementation AQbD depends on the target measurement which comprises the product file in the form of ATP (analytical target profile) and CQA (ATP is the analogue of QTPP in product design), followed by an understanding on selection of suitable analytical technique, risk assessment for variables, method development using DoE, and validation process for model and control strategy.

**ANALYTICAL TARGET PROFILE**

In AQbD, Analytical Target Profile (ATP) is analogous to Quality Target Product Profile (QTPP) element in QbD. ATP is a tool for method development, resulting in achieve of QTPP. It describes the method requirements which are expected to be measured. Recently PhRMA and EFPIA defined ATP as: “ATP is a statement that defines the method’s purpose which is used to drive method selection, design, and development activities.”\textsuperscript{[12]} Another definition of ATP as given by USP council of experts is, “the objective of the test and quality requirements, including the expected level of confidence, for the reportable result that allows the correct conclusion to be drawn regarding the attributes of the material that is being measured”.\textsuperscript{[12]} 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 can be regarded as the focal point for all stages of the analytical life cycle.\textsuperscript{[13]} ATP is not limited to method development only, but also met during method transfer and lifecycle management. Also, ATP is not always limited to single method and more than one method analytical technique can satisfy the same ATP. For the future aspects, the ATP concept may be a means of proposing more advanced regulatory approaches to method submission and review.\textsuperscript{[14]} In pharmaceutical industry, internal change control management system is responsible for effective implementation of ATP to provide regulatory flexibility.\textsuperscript{[15,16]}
FIG 1: factor involved in effective outlining of analytical target profile

ANALYTICAL METHOD PERFORMANCE CHARACTERISTICS

Analytical method performance characteristics are defined to meet the need of analytical target profile. There are two types of method performance, that is, systematic (bias) and inherent random (variable) components. In chromatographic sepration, USP and ICH have listed many validation parameters, which are considered as method performance characteristics. Among these parameters, accuracy and precision are commonly considered as method performance characteristics to quantify the substances. It is assumed that no method can be accurate and precise without adequate specificity, linearity, and peak resolution. However, these performance characteristics do not represent robust behavior of the method. Range is also an important parameter that has to be establish based on acceptable behavior of both systematic and random performance characteristics. But both range and robustness are neither categorized as systematic variability nor categorized as random variability. Other characteristics such as linearity and specificity are not needed to be incorporated in the ATP, as they are not directly linked to understand the agreement of a measurement with the true value. Based on acceptable behavior of both systematic and random performance characteristics range should be established. Precision, detection limit, and quantification limit have been described as parameters for Inherent random variability. However range and robustness have not been listed in these guidelines.
SELECTION OF ANALYTICAL TECHNIQUES
This is done with reference to the needs, which are defined in the ATP. In other side, the selected analytical technique should satisfy the required method validation parameters as required by regulatory requirement. For example, specificity may not be included in ATP, but the analytical technique should satisfy the specificity. Hence chromatographic method can satisfy the required method performance defined in ATP and validation requirement of ICH. Instead the UV spectrophotometric method can fulfill the needs of ATP but may not satisfy ICH Q2.[17]

RISK ASSESSMENT
Risk assessment identifies the critical method variables, the parameters that impact the ATP. Once the technique is identified, AQbD focuses on method development and includes detailed assessment of the risks associated with variability such as analyst methods, instrument configuration, measurement and method parameters, sample characteristics, sample preparation, and environmental conditions. Traditional method development was based on testing the method after transfer whereas Analytical QbD necessitates the risk assessment step before method transfer and throughout the product life cycle. Risk assessment strategy needs to fulfill the ICH Q9 guideline: “it is systematic process for the assessment, control, communication and review of risks to the quality across the product lifecycle”. [18] Fig 2 describes different steps involved in Risk Assessment.[19] The terminologies used in the diagram are discussed as follows.

Fig 2: A pictorial sequence of steps involved in Risk Assessment and the various tools involved in the process.
The first step Risk Identification is important to identify and prioritize potential risks. These risks could be method of operation of instrument, characteristics of reagent, cycle time etc. Flow charts and check lists are utilized to identify risk factors. Second step in the process is Risk Analysis. Tools which are employed in this step include Ishikawa Fishbone Diagram and the CNX approach. Cause and Effect diagram or the Ishikawa Fishbone diagram compartmentalizes the risks into different categories depending on their source. The other tool is the CNX approach where C indicates the high risk factors, N represents the potential noise factors and X is the factors which are to be experimented upon. According to this approach the risk factors are classified into the following categories: \textsuperscript{[20]}

- **High Risk Factors**: eg. sample preparation methodology. These are to be fixed during the
- **Method Development process.**

- **Noise Factors**
  - These are subject to an MSA study. Done through staggered cross nested study design and variability plots. These factors are subjected to robustness testing.

- **Experimental Factors**
  - eg Instrumentation and operation methods. Subjected to ruggedness testing and acceptable range is identified. The third step is Risk Evaluation which is done through Failure mode and effects anlysis (FMEA) and the Matrix designs. An equation correlating Risk Factor and occurrence is as follows: \textsuperscript{[21]}

  \[
  \text{Risk factor} = \text{Severity} \times \text{Occurrence} \times \text{Detectability}
  \]

Where,

Severity = effect on patient related to safety or efficacy (CQAs).
Occurrence = chance of failure related to product, process knowledge, and control.
Detectability = ability to detect a failure capability of analytical method and sampling.

**DESIGN OF EXPERIMENT**

In harmony with the requirement of ICH Q8 guidelines, concerning “design space” in product development, method operable design region (MODR) could be established in method development phase, 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 CQAs) that produces results which consistent with 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 without resubmission to FDA. There are many analytical works which have been reported using experimental design based on factorial or fractional factorial design or response surface methodology. Data are collected and software is generated by entering obtained results in terms of values from actual experiments. Then that data base is generated which helps to predict the effect of various chromatographic conditions in large number. This type of software helps to predict outcome without actual experimentation. Response from design also includes resolution and run time.[19] Therefore this automated approach is cost effective and saves time. DoE in AQbD approach includes the following activities which are listed as follows:[9]

1. Screening – Screening is done to identify various Critical Method Parameters (CMP) which are considered in optimization experiment. The various tools and selection approach are shown in table-2 given below.

Table 2: Selection of DOE tools in analytical quality by design.

<table>
<thead>
<tr>
<th>Design</th>
<th>Number of variables and usage</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full factorial design</td>
<td>Optimization/2–5 variables</td>
<td>Identify the main and interaction effect without any mix up.</td>
<td>Experimental runs increase with increase in number of variables</td>
</tr>
<tr>
<td>Fractional factorial design or Taguchi methods</td>
<td>Optimization/and screening variables</td>
<td>Requiring lower number of experimental runs</td>
<td>Resolving mix up effects of interactions is a difficult job</td>
</tr>
<tr>
<td>Plackett-Burman method</td>
<td>Screening/or identifying vital few factors from large number of variables</td>
<td>Requiring very few runs for large number of variables</td>
<td>It does not unveil interaction effect</td>
</tr>
<tr>
<td>Pseudo-Monte Carlo sampling (pseudorandom sampling) method</td>
<td>Quantitative risk analysis/optimization</td>
<td>Behavior and changes to the model could be investigated with great ease and speed. This is preferred where exact calculation is possible</td>
<td>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 algorithm</td>
</tr>
<tr>
<td>Full factorial design</td>
<td>Optimization/2–5 variables</td>
<td>Identifying the main and interaction effect without any confusion</td>
<td>Experimental runs increase with increase in number of variables</td>
</tr>
</tbody>
</table>
2. Optimization –In this step, Quantitative measures for critical method in variables (i.e., CMP) which were identified either from screening or from risk assessment can be incorporated.

3. Selection of DoE tools: The choice 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. Statistical knowledge is main importance to interpret the interaction and contribution of variables in method responses, which serves as a tool to select the variables at optimum levels. A typical selection of DoE tool are shown in above tableX. Taguchi method can be used with lower number of experimental runs compared to factorial designs but the interactions confounded need to be resolved. Placket-Burman method are used to studied large numbers of input variables without interaction effects.

4. MODR- MODR could be selected by creating contour plots(2D plots) using mathematical models. 2D contour plots are generated for non-linear and the relationship between input variable and method response is having more curvature effect. There are surface model available for linear data as well.

5. Model Validation: Prior to the choice from contour or graph, the predicted values for the targeted method response has to be validated by actual experimental run. Subsequently, regression analysis has to be carried out to validate the design statistically.

**METHOD QUALIFICATION**

Once method development and risk assessment has been done the subsequent step is method qualification. It is a onetime activity and generally occurs before method transfer in order to provide assurance that a suitable and reproducible method has been developed. ICHQ2 (R1) guidelines are pursued for method qualification or validation of analytical method which comprising set of variables. This is to be done under normal operating conditions. The design qualification of an operation typically includes operation qualification, process qualification and installation qualification. In addition to method validation as per regulatory guidance, method verification could be performed through a joint accuracy and precision assessment at different method factor points within the chromatographic separation space (from MODR). Multipoint verification within MODR make sure the greatest probability of the ability of the method to meet the requirement in ATP. [13]
CONTROL STATREGY

In product QbD, control strategy is planned to make sure the instant product production with required quality. Control strategy is obtained from various data collected during method development phase and method verification process. The strategy is data dependent. Data generated during method development and method verification forms the basis of the control strategy. This data correlation will predict the ability of method to meet the goal of ATP criteria and control strategy, including the overall monitor of method parameters that significantly influence method (variability). It is noted that method control strategy of AQbD approach does not differ from the traditional control strategy. However, method controls require to be confirmed to ensure relation between method purpose and method performance.[18]

LIFE CYCLE MANAGEMENT

Life Cycle Management is a form of continuous assessment which is necessary to established of an analytical method for quality control or routine testing over the time to ensure that the analytical method remains compliant with the goal described ATP. It begins with articulation of ATP and continues throughout life cycle of the analytical operation. This continuous monitoring allows an analyst to detect, identify, and address any abnormal or out-of-trend performance of the analytical method. Knowledge gained from risk assessment and data collected from DoE could be used as the repository of knowledge to make justified changes wherever required. This reiterates the importance of creation and maintenance of knowledge space.[22]

PAT and AQbD

For the effective implementation of process analytical technology (PAT) system, parallel development of analytical QbD is highly suggested. PAT is based on two significant components:

(a) Knowledge of the scientific and engineering principles involved manufacturing process;
(b) Understanding of the variables which affect product quality. According to the FDA draft guidance, "the desired state of manufacturing which is a product quality and performance are ensured by the design of effective and efficient manufacturing processin which continuous quality assurance was recommended. Once the properties of the drug product components are understood, the processing variables that control the pertinent 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.\textsuperscript{[18]}

APPLICATION
Some benefits of implementing “Quality by Design” For FDA submissions include:

1. Enhanced scientific foundation for review
2. Provides for better coordination across review, compliance and inspection
3. Improves information in regulatory submissions
4. Provides for better consistency
5. Improves quality of review (establishing a QMS for CMC)
6. Provides for more flexibility in decision making
7. Ensures decisions made on science and not on empirical information
8. Involves various disciplines in decision making
9. Uses resources to address higher risks QbD can be applied for various analytical methods which include,\textsuperscript{[20]}

1. Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals).
2. Hyphenated technique like LC–MS.
3. Advanced techniques like mass spectroscopy, UPLC, and capillary electrophoresis.
4. Karl Fischer titration for determination of moisture content.
5. Vibrational spectroscopy for identification and quantification of compounds e.g. UV method.
6. Analysis of genotoxic impurity.
7. Dissolution studies.

CONCLUSION
The field of analytical QbD is likely to continue to develop within the pharmaceutical industry, as favorable results have already been realized from its application. However, the AQbd process is facing certain hindrances. Primarily, there is insufficient understanding of Quality by Design process for Analytical techniques in the pharmaceutical industry. Therefore, investment in developing human resources and enhancing the understanding of the AQbD process through training and education is necessary. In terms of the regulatory aspect, there needs to be clear definitions of the different Analytical QbD elements. It is also accept that the review process of FDA is inconsistent when it comes to a QbD application. This
perception discourages the adoption of QbD approach. It is time that all the imperfection are worked out and AQbD approach is embraced and implemented globally. There needs to be steadfast commitment on the part of the pharmaceutical industry for this approach to succeed.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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