REVIEW

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ANALYTICAL QUALITY by DESIGN – A REVIEW

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ABSTRACT

Analytical methods are required to be developed at different stages of the pharmaceutical product life cycle. These activities if properly not streamlined based on the knowledge of science and process understanding may lead to a very costly and time consuming procedure. Pharmaceutical industries are striving for new policy or new element which can be added or replace the existing elements of quality and risk management system. A well known quality expert Joseph M. Juran first outlined the concept of Quality by Design. (QbD). The concept of QbD can be extended to analytical method development known as AQbD. Quality by Design is a systematic approach to development that begins with predefined objects and emphasises product and process understanding and process control.Analytical Quality by design is a vital part of the modern approach towards a method development and helps in the systematic approach to drug development. The main objective of the present review article is to describe different steps involved in method development by AQbD along with addressing the concerns related to its implementation. The approach for an analytical method development includes ATP (Analytical Target Profile), CPAs (Critical Performance Attributes), MODR (Method Operable Design Region), Analytical Method Validation, Control Strategy, Continual Method Improvement.

KEY WORDS: Analytical Quality by Design, Analytical Target Profile, Critical Performance Attributes, Method Operable Design Region.

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INTRODUCTION

Quality-by-design (Qbd) has become an important standard in the pharmaceutical industry since it was introduced by the US Food and Drug Administration. For any entity, quality is one of the basic criteria in addition to safety and efficacy to be accepted and approved as a drug. The quality is the suitability of either a drug substance or a drug product for its intended use.[2].

Analytical methods are required to be developed and validated during a pharmaceutical manufacturing, as it plays a very pivotal role in product development. A robust , accurate, precise analytical method not only satisfy whether the quality of drug is achieved as per the intended therapeutic use but also serves as a purity check at each stage of product development life cycle. The carelessness in this may lead to a very costly and time consuming procedure. During a method development ruggedness and robustness should be established early to make certain method performances over the lifetime.In present days, analytical method failure is becoming more common especially during method transfer. The formation of design space by QbD approach determines a suitable method control that delivers its intended space and also it eliminates batch failure, increases efficiency and cost effective. [3]

According to ICH Q8 guidelines, QBD can be defined 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."[4]

Table 1: HISTORICAL BACHGROUND of QbD[5-7]

YEAR	ACTIVITIES
1950	Operation windows
1970	QBD created by Joseph M Juran
Sept 2002	QBD concept integrated by USFDA in cGMP
Sept 2004	USFDA release final report in "Pharmaceutical cGMP"
Sept 2004	USFDA Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Control
Nov 2009	ICH: Q8(R2) Pharmaceutical Development
Nov 2005	ICH: Q9 Quality Risk Management
June 2008	ICH: Q10 Pharmaceutical Quality System

APPLICATIONS of AQbD[8]

Analytical Research Development

Advanced level of method understanding for each critical factor with Method Operable Design Region will provide flexibility for method transfer from AR&D to QC, Reduction in variability in analytical attributes for improving the method robustness.

Manufacturing Plant & Quality Control

Detailed idea through model predicting how product will behave with changes in each CMAs

and CPPs adjustable within design space along with other QbD tools.

Quality Assurance

Investigation of variability or batch failure will become easier, efficient and speedy for root cause analysis through Quality Risk Management during development, Eliminate batch failures, Minimise deviations and costly investigations.

Regulatory Affairs

Review and Approval process will become very easy and speedy. Moreover developed and verified design space will provide regulatory flexibility for post approval change management.

What is Analytical Quality by Design? [9-10]

The introduction of AQbD has made the industry to look beyond quality by testing (QbT) for ensuring product quality and performance. The knowledge acquired during development may support the formation of a design space and determines suitable process controls. Analogous to process QbD, the result of AQbD is a well understood, fit for purpose, and robust method that consistently delivers the intended performance throughout its lifecycle. AQbD helps the scientific understanding of pharmaceutical process and method and the critical quality attributes are identified and their effect on final quality of product is analyzed. Along with providing required design space for development, also allows the continuous improvement till finished steps of method.It avoids regulatory compliance problems with reduced deviations and scientific variations , improving the robustness.

Use of chromatographic analytical techniques such as High performance liquid chromatography (HPLC), Gas chromatography (GC), High performance thin layer chromatography (HPTLC), super critical fluid chromatography (SFC): are very widely known as they have various advantages over other non-chromatographic methods. They are versatile, robust, and require fewer amounts of samples. With the use of automation these techniques minimize the probability of human error.

Table 2: DIFFERENCE BETWEEN REGULATORY PERSPECTIVE OF QbD and AQbD[11]

Product Quality by Design (QbD)	Analytical Quality by Design (AQbD)
Quality Target Profile **(QTPP)** Definition	Analytical Target Profile (**ATP**) Definition
Critical Quality Attributes **(CQA)**	Critical Performance Attributes **(CPA)**
Risk Assessment of Critical Material Attributes and Critical Processing Parameters	Risk Assessment of Critical Method Attributes and Critical Method Parameters
Designing of Experiments and Development of Design Space**(DS)**	Designing of Experiments and Development of Method Operable Design Region **(MODR)**
Manufacturing Process Validation	Analytical Method Validation
Implementation of Control Strategy	Implementation of Control Strategy
Continual Process Improvement	Continual Method Improvement

ELEMENTS OF AQbD[12]

Fig. 1 Elements of QbD

ANALYTICAL TARGET PROFILE (ATP):

ATP is the the initial step taking into account systematic variability, inherent variability, & system suitability for method development and has been mentioned in the ICH Q8 R(2) guidelines. Inspite of analytical specifications, during the method development,the method is likely to experience a number of changes brought through unintentional deviations, continuous improvement activities or the need to operate the method and\or process in a different environment.ATP is the recognition and the selection of method target analytes (product and impurities), which are likely to affect the method performance at any stage of the method development . The target could be API and impurities, type of analytical technique , analyst, lab environment, equipment, method operation .[13]

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, range, sensitivity, and the associated performance criterion).

The common ATP's of an instrument like LC-MS/MS could be noise, heat block temperature, buffer pH, flow rate, column temperature etc.[14-15]

CPA (Critical Performance Attributes)

ICH Q8 (8) defines CQA or CPA as a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.[16]

In this step, the analyst has to identify the critical method parameters that directly affects the method performance. The CPA's will differ from project to project . Critical method parameters (CMP's) are divided into three types' viz. parameters regarding analyte, parameters regarding instrument and parameters regarding operation conditions. Typical CPA's for chromatographic experiments are sampling, sample preparation, standards, reagents, column

chemistry, mobile phase composition, pH and flow of mobile phase, column temperature, detector selection etc. CQA's (responses) for the above parameters would be resolution, retention time, tailing factor, detection limit, robustness.

Physical and chemical properties of the drug substance and impurities such as polarity, charged functional groups, solubility, pH value, boiling point, and solution stability also describe CQA for analytical method development.[17]

Risk Assessment

According to ICHQ9 guideline: "it is systematic process for the assessment, control, communication and review of risks to the quality across the method development". This step is vital in order to reach a confidence level that the method is reliable. Once the ATP and CPA are identified, AQbD emphases on detailed risk assessment of the factors that may lead to possible variability in the method, like analyst methods, instrument configuration, measurement and method parameters, sample characteristics, sample preparation, and environmental conditions.

According to ICH Q9, risk assessment can be carried out in three steps viz., risk identification, risk analysis and risk evaluation.Risk Assessment can be performed from initial stage of method development to continuous method monitoring [18-19] .

Risk identification

Ishikawa Fishbone Diagram

The risk can be identified by Ishikawa Fishbone diagram by categorising the factors according to the source and find out the causes and the effect of the selected factors to the method performance . It can also be identified by SIPOC by identifying the potential gap between (S= supplier, I- input, P= high level process, O= output, C= customer).[20]

Risk Analysis

The analysis of the risk which can be can be performed by Relative Risk Matrix Analysis and Failure Modes Effects Analysis methods.

Relative Risk Matrix Analysis

The first step in the relative risk matrix analysis is to categorise and prioritize the selected ATP's according to low, medium and high risks on the CPA. These risks could be method of operation of instrument, characteristics of reagent, cycle time etc. The low risks can be broadly accepted and no further investigation is required. More attention is given to the the medium and high risk factors which are unacceptable and further investigations are needed to reduce the risk.

Failure Mode Effect Analysis.

This is the another way of risk analysis .In this process, the risks are given a number on a scale of 1 to 5 , based on the severity , occurrence and detection, which on multiplying gives the Risk Priority Number. Then a bar graph is being plotted , considering RPN as the y-axis and the method attributes/factors as the x-axis.. As per RPNs, all the factors are arranged in decreasing order by Pareto Chart & High Risk Factors are categorized as 'Critical'. Method Attributes which got RPN more than 25 are given highest priority among all the risks, they should be taken into consideration as most Critical Material Attributes of API , which were required to be optimized &/or controlled.

Method Operable Design Region

MODR is a systematic series of experiments, in which purposeful changes are made to input factors to identify causes for significant changes in the output responses and determining the relationship between factors & responses to evaluate all the potential factors simultaneously, systematically and speedily.

Method operable design region (MODR) can also be established in method development phase, which could serve as a source for robust and cost effective method.It is the operating range for the critical method input variable that produces results which consistently meet the goals set out in the ATP. MODR permits the flexibility in various input method parametersto provide the expected method performance criteria and method response without resubmission to FDA. Once this is defined, appropriate method controls can be put in place and verification and method validation can be carried out.

If the factors are more than 4,first the critical factors has to be screened out by screening designs and then optimised by the optimization designs . If the number of factors are less than 4, it can be directly optimized by the optimization designs.[21-22]

Selection of Designs :

a) **Screening**

In screening, qualitative input variables can be screened out. It identifies the various critical method parameters (CMP) to be considered in the optimization experiments. When the goal is to screen numerous factors, fractional factorial design or plackett burmann designs can be used . If the factors are more than four but less than six, then the fractional factorial design can be opted and when the factors are more than six then Plackett Burmann design can be used.

b) **Optimization**

For optimization we can select, factorial designs, response surface and mixture designs. When the goal is to evaluate the main effects and the interactions between the factors, and the factors are more than 2 and less than five , then full factorial designs can be selected. When the goal is optimisation of known individual critical factors, and the factors are limited to two to four, then response surface designs are selected. When the goal optimization of ratio of critical components in mixture and factors are component of a mixture, then mixture designs are selected. The response surface includes box behnken design and central composite design and the mixture design includes simple lattice and constrained mixture. After selection of experimental design, dependent responses (CPAs) are measured for all Experimental Runs for different combination of factors to be studied. After evaluation of model, of all the responses should be specified for numerical & graphical optimization of all the factors .

Selection of model:

After all Experimental Runs, a analysis of model (a mathematical relationship between factors & response), should be selected which depends on the shape of the expected response behaviour. It could be linear, quadratic, cubic, scheffe. For Selection of Model, ANOVA should be carried out thoroughly for testing of significance of each Model with Lack of Fit & Goodness of Fit Statistics. In this the f value, p value , precision value and R^2 adjusted and predicted are to be studied.

Interpretation of model graphs:

Model Graphs will give clear picture of how the response will behave at different levels of factors at a time through predicted response equation with individual coefficients which includes a)1D interaction: it shows the linear effect of changing the level of a single factor. B)2D contour: reveals effect of 2 independant factors on one response at a time.c)3D surface : it reveals the effect of and 4D cube.

After Development of Design Space, Minimum of 3 Confirmatory Experimental Runs should be conducted within defined range of design space for Verification of the Design Space. The

Observed Results of these confirmatory runs will be compared with Predicted Results from Model Prediction equation by means of Correlation Coefficient R2 which should be not less than 0.9.[23]

Control Strategy

A planned set of controls for CMAs & CMVs-derived from current detailed method development during lab scale developmental stage ensures method performance and product quality. The control strategy is an integrated overview of how quality is assured based on current process and product knowledge.This phase also includes eventual replication of optimized experiments, data collection and analysis to assure that the method remains in the state of control.[24]

Product life cycle by continual improvement

If any unexpected method variability is detected, appropriate actions will be taken to correct, anticipate, and prevent future problems so that the process remains in control.[25]

CONCLUSION

An accurate data analysis tool is necessary to evaluate any process or system to assure that it works consistently as intended. Implementing QbD is one of the approaches that devoutly make scientist to understand the process or system closely. Optimizing process by QbD has become mandatory by some of the regulatory guidelines around the globe. The outcome of AQbD is the understanding from method development to method transfer. AQbD tools are ATP, CPA, Method Optimization and Development with DoE, MODR, and Control Strategy with Risk Assessment, Method validation, and continuous improvement. QbD has gain importance in the area of pharmaceutical processes like drug development, formulations, analytical method and biopharmaceuticals.

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