International Journal of Scientific Research and Reviews

The Impact of Analytical Quality by Design (AQBD) In the Method Development of Liquid Chromatography for Quality Control of Pharmaceuticals: A Review

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ABSTRACT

The objective of this review article is to provide a comprehensive understanding on different steps of AQbD, along with their concern ICH guidelines. The concepts of quality by design are described in ICH Q8-Q10, which have also been applied to analytical methods. Analytical quality by design Analytical involves following steps: Analytical target profile (ATP) critical quality attribute (CQA), critical process parameters (CPP), Risk assessment: (failure mode effects analysis -FMEA , Ishikawa diagrams-fishbone diagrams), design of experiment (DOE), ANOVA has been perform to identify the significant and insignificant factors using design expert software, design space (DS) and control strategy, and PAT. The application of QbD principles to analytical method development is focused on the concept of building quality into the method during development, instead of testing methods for quality after development. The aim of pharmaceutical development (ICH Q8) is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space**, specifications, and manufacturing controls. The ICH Q 9 guideline provides principles and example of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. The objective of ICH Q10 is the implementation of the Q 10 model should result in achievement of three main objectives which complement or enhance regional GMP requirement.

KEYWORDS: AQbD, ICH, ATP, DS, CQA's

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INTRODUCTION

Quality by design is a concept first outlined by quality expert Joseph M. Juran in publications, most notably juran on quality by design. It is a systematic approach to development that begins with predefined objectives and emphasizes product. Process understanding and process control based on echo knowledge and quality risk management. The same QbD principles have been applied to the development of analytical methods, and are termed Analytical QbD (AQbD). Analogous to process QbD, the outcome of A QbD is a well understood, fit for purpose, and robust method that consistently delivers the intended performance throughout its lifecycle. The broad knowledge obtained from this 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. A very useful component of QbD is the understanding of factors and their interaction effects by a desired set of experiments. For the purpose of QbD for HPLC methods, robustness and ruggedness should be verified early in the method development stage to ensure method performance over the lifetime of the product.

GUIDELINES GIVEN BY ICH FOR QBD

ICH Guidelines:[1,2,3]

QbD ultimately helps to implement Q8 and Q9. Recently, the US Food and Drug Administration introduced quality by design (QbD) as a fundamental pharmaceutical quality model to be considered in the development of pharmaceutical products and processes. QbD principles have also been supported by International Conference on Harmonization (ICH) guidelines Q8 (R2), Q9, and Q10. ICH Q8 (R2) guideline provide an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management (for definition, see ICH Q9) to the development of a product and its manufacturing process.

ICH Q9(quality risk management) guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

ICH Q10 guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances (i.e. API) and drug products, including biotechnology and biological products, throughout the product lifecycle.

The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the differences among, and the different goals of each stage (see Section 3).

For the purposes of this guideline, the product lifecycle includes the following technical activities for new and existing products:

• Pharmaceutical Development:
  ✓ Drug substance development;
  ✓ Formulation development (including container/closure system);
  ✓ Manufacture of investigational products;
  ✓ Delivery system development (where relevant);
  ✓ Manufacturing process development and scale-up;
  ✓ Analytical method development.

• Technology Transfer:
  ✓ New product transfers during Development through Manufacturing;
  ✓ Transfers within or between manufacturing and testing sites for marketed products.

• Commercial Manufacturing:
  ✓ Acquisition and control of materials;
  ✓ Provision of facilities, utilities, and equipment;
  ✓ Production (including packaging and labeling);
  ✓ Quality control and assurance;
  ✓ Release;
  ✓ Storage;
  ✓ Distribution (excluding wholesaler activities)

Element of Qbd in Analytical Method:

➢ Analytical Target Profile (ATP)
➢ Critical Quality Attribute (CQA)
➢ Method Design
➢ Critical Process Parameters (CPP)
➢ Risk Assessment
➢ Design Space(DS)
➢ Design of Experiment (DoE)

ANALYTICAL TARGET PROFILE (ATP)[4]

''QbD is a systematic approach to product and process design and development,'' Hence it begins with determination of goal or method intent. In this emphasis is given on the product and process understanding ATP is way for method development or it is simply a tool for method development. It describes the method requirements which are expected to be measured. In general the goal of the chromatographic method is separation, quantification and identification of the method requirements will be the accuracy precision, robustness, ruggedness and so on as described in ICH guideline

THE ANALYTICAL TARGET PROFILE (ATP) OF ANALYTICAL METHOD IS,

- Method should produce good elution at minimum retention time.
- It should be accurate, linear, precise, robust and quantitative.
- The peak signal should be free from interference with acceptable signal to noise ratio.
- In case of drug combination or drug-related substance studies the resolution should be more than 1.75.

  There are number factors which can affect quality and lead to failure to meet QTPP.

  These are listed below,

Method design related factors

- Flow rate
- Temperature
- Mobile Phase composition
- pH
- Nature of drug
- Drug mobile phase interaction
- Environmental conditions
- Type of method

Instrumental factors

- Type of instrument
- Type of column
- Column dimensions
- Column packing material
- System to system variability
- Instrument efficiency/ failure

Material

- Raw material sources
- Solvent grades

Personnel related

- Analyst to analyst variation
- Human error

All these factors are to be considered while developing analytical method. The factors are first categorized based on their impact on quality. The factors are classified as **critical, non-critical and unclassified.**

❖ CRITICAL QUALITY ATTRIBUTE (CQA'S)[4]

A critical process parameter (CPP) is any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency. A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the QTPP. CQA for analytical methods includes method attributes and method parameters. Each analytical technique has different CQA. HPLC (UV or RID) CQA are mobile phase buffer, pH, diluents, column selection, organic modifier, and elution method. GC methods CQA are gas flow, oven temperature and program, injection temperature, sample diluents, and concentration. HPTLC method CQA is TLC plate, mobile phase, injection concentration and volume, plate development time, color development reagent, and detection method. Nature of impurities and DS can define the CQA for analytical method development such as solubility, pH value, and polarity, charged functional groups, boiling point, and solution stability.

❖ METHOD DESIGN

Method design is prepared for appropriate availability of material and setting various experimental conditions. In this reagents required are made available. Regional and geographical conditions are taken into consideration. Feasibility of instruments is checked and experimental design is prepared. In this use of various flowcharts decision tree can be made for correct implementation. In case of HPLC method developments scouting is done. In this large number of experimental conditions were tried (pH, temperature, columns, and buffers). Data is generated by entering obtained results in term of values from actual experiments. Then 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 deign also includes resolution and run time. Hence it is cost effective as well as time effective. The software

also assists the future changes in method. Method design also involve selection of different analytical techniques that can be opt like HPLC, LC, Raman and most effective method amongst it chosen. Among various methods; suitable method to serve the desired purpose is chosen. For example, to determine the impurities, HPLC with detector like PDA can be used. In the method design, a method that meets method requirement is established. Method design may be repeated or modified as and when required throughout the lifecycle. Method design should be done according to standardized approach. This approach helps in method transfer step from research to quality control department. Method development strategy (MDS) includes Design of experiment (DoE). It is helpful in risk assessment by gaining knowledge about existing method and allows for effective control strategies for critical parameter.

❖ CRITICAL PROCESS PARAMETERS: [5]

Critical process parameters (CPPs) are defined as parameter whose variability have an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality, and this statement can be fit perfectly to analytical methods or A critical process parameter (CPP) is any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency. A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the QTPP. Parameters are classified into three categories: unclassified, critical or non-critical. The criticality of an unclassified parameter is undetermined or unknown, whereas a parameter is critical when a change in that parameter can cause the product to fail to meet the ATP. Development studies should be able to move unclassified parameter to either non-critical or critical; otherwise they may need to be constrained at fixed values or narrow ranges because they might be critical.

In the framework of method development, DS can be considered as a zone of theoretical robustness as no drastic changes in the level of the CQAs of the method should observed. Hence, to define an analytical DS, a widely selected number of factors, also called critical process parameter (CPP) - operating factors (eg. Gradient time) in chromatography that impact on the analytical technique under development has to be studied simultaneously.

❖ RISK ASSESSMENT[2]

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool and the types of information needed to address the risk question

will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

According to ICH Q9 risk assessment can be done in three steps, viz. risk identification, risk analysis and risk evaluation. Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders.

Risk analysis Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detestability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.
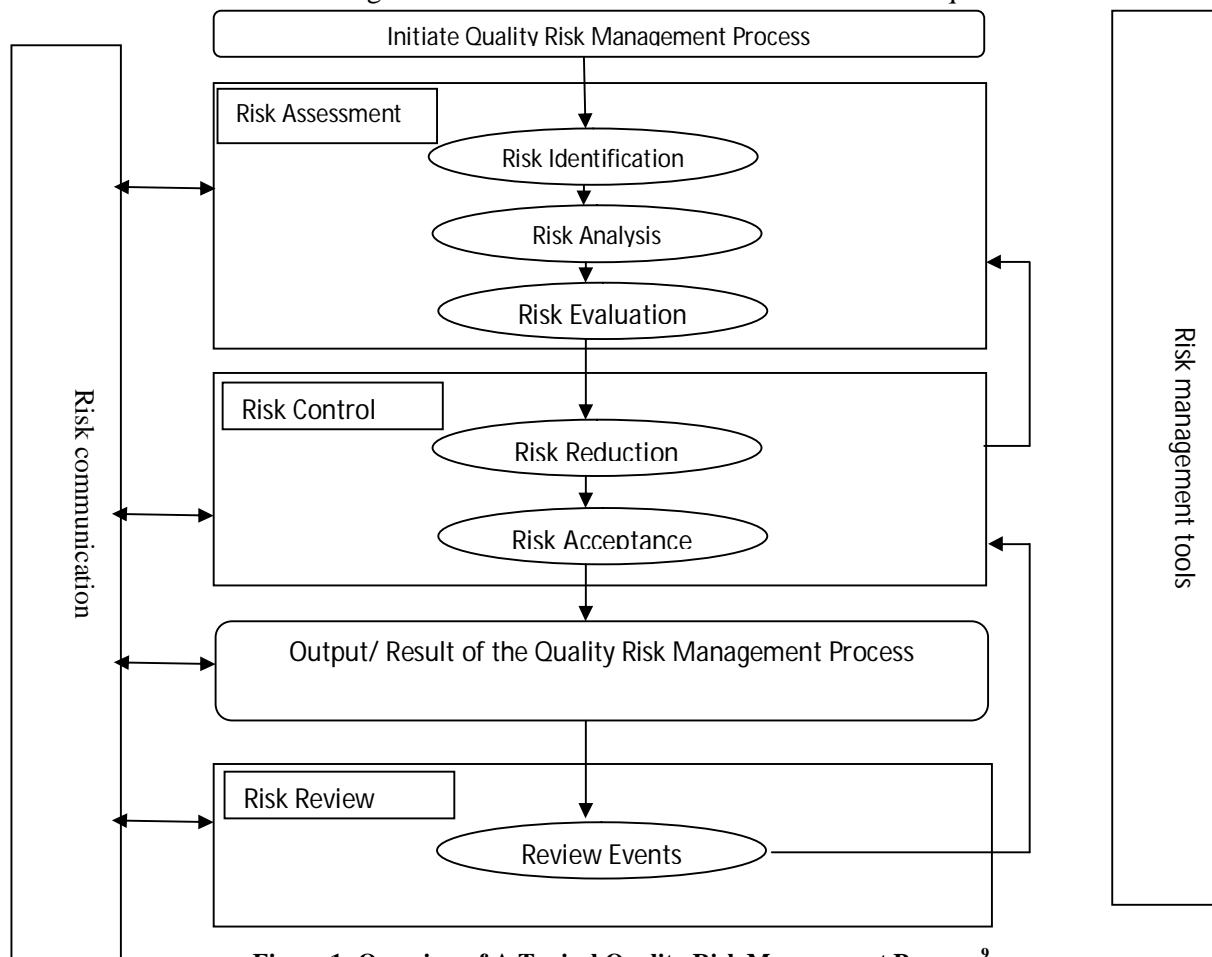

Figure 1: Overview of A Typical Quality Risk Management Process [9]

There are two risk assessment tools for AQbD.

- Failure Mode Effects Analysis (FMEA)
- Ishikawa diagram (Fishbone diagram)

a) FAILURE MODE EFFECTS ANALYSIS (FMEA)

FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding

POTENTIAL AREAS OF USE(S)

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities. FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/ results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

b) ISHIKAWA DIAGRAM (FISHBONE DIAGRAM)[9]

Ishikawa diagram segregate risks into different categories, for example those associated with instrumentation, material, methods, measurement, laboratory climate, and human factors. An Ishikawa diagram for an HPLC assay and impurities method was presented, highlighting the different sources of factors, followed by a CNX analysis to decide which factors should be controlled (c) these were the potential noise (N) factors and on which experiments (X) should be conducted to determine acceptable ranges.
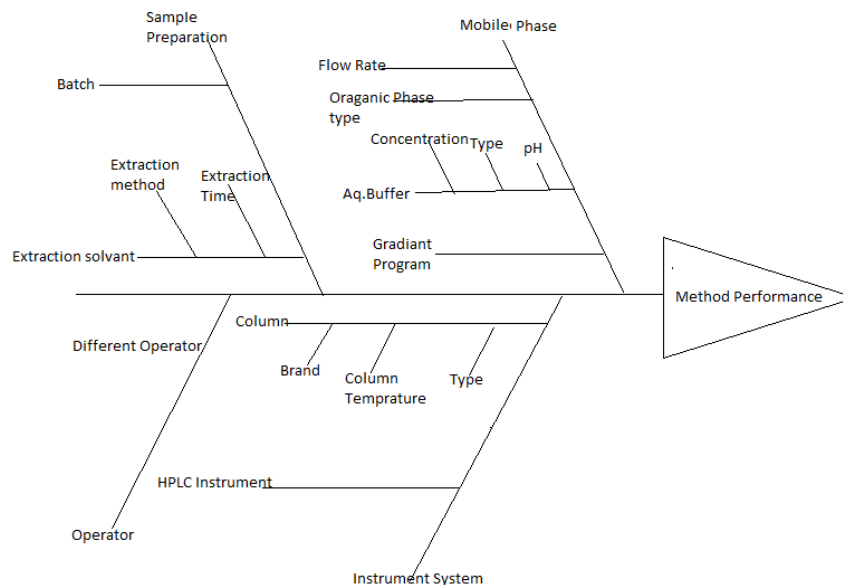

Figure No.2: Ishikawa Diagram Or Fishbone Diagram For Risk Assessment Study

❖ **DESIGN OF EXPERIMENT**

Here you would define factors, define response, create design construct model, evaluate the model, interpret the result & accordingly make the decisions. One can make use of DoE software for AMD too. Traditionally we are used to single variant study. Here DoE help to do multivariate analysis e.g. wavelength, flow rate, sample concentration in HPLC and its impact on retention time, resolution, total run time, column performance etc. accordingly software can through the best fit equation including design space and near operating range. All factors that can influence the performance of analytical method can be mapped against unit operation within the method. Here the analyst needs to be trained basic statistic too. Depending upon the complexity, one can use full factorial design, the level can be varied.

FACTORIAL DESIGN

Factorial design is used in experiments where the effect of different factor, or conditions, on experimental result is to be elucidated. Factorial designs are the designs of choice for simultaneous determination of the effects of several factors are their interactions.

BOX BEHNKEN DESIGN [6]

Box and Behnken (1960) derive a series of 3 level second order designs that has been very popular, especially for a small number of factors. For t =3 factors, the box-behnken (BB) design requires only 12 runs, plus a recommended n0=3 centre point runs. The comparable central composite design requires 14 runs in addition to the centre point replicates. For t=4,BB and central composite designs are of equal sizes, 24+n0. BB (1960) contains only 10 designs, one each for t=3,4,5,6,7,8,9,10,11,12, and 16. An earlier technical report (BB 1958) contains 7 additional designs, including a couple of designs for t=8, although these additional designs have large redundancy factor, defined by BB as the ratio of the number of factorial runs to the numbers of parameters.

❖ **DESIGN SPACE: [1]**

In ICH pharmaceutical-development guideline Q8, the DS is defined as the multidimensional combination and interaction of input variables (eg. Material attributes) and process parameters that have been demonstrated to provide assurance of quality. Therefore, the multidimensional combination and interaction of input variable corresponds to subspace, so called the DS, where assurance of quality has been proved. The DS is necessarily encompassed within the experimental domain, which is the multidimensional space formed by the factor ranges used during method development. The main concept lying behind the ICH Q8 definition of DS is assurance of quality (also known as quality risk management).

In the framework of method development, DS can be considered as a zone of theoretical robustness as no drastic changes in the levels of the CQAs of the, method should be observed. Hence, to define an analytical DS, a widely selected number of factors, also called Critical Process Parameter (CPP)-operating factor. (e.g. Gradient time in chromatography) that impact on the analytical technique under development have to be studied simultaneously. Usually, the CPPs are obtained from a risk analysis and a prioritization strategy. The analytical DS is finally a multivariate domain of input factors ensuring that critically chosen responses are included within predefined limits with an acceptable level of probability. In order to define the DS of analytical methods; several steps have to be performed. The starting point is to gather and to review all historical information available on the analytical method under development.

❖ METHOD OPERABLE DESIGN REGION (MODR) [5]

MODR of any analytical method, also termed as Analytical Design Space (ADS), or Proven Acceptable Range (PAR), is the multidimensional combination and interaction input variable (i.e. CMVs during analysis) that have been demonstrated to provide assurance of quality. Once the MODR is established with the help of experimental design, overlay plotting, and/or numerical techniques of desirability function, it is validated to identify the edge of failures. Within the MODR, many a times, it is ideal to identify a region for setting in-house specifications within the firms working environment , also called as Normal Operating Range(NOR) or analytical control space. The fruition of any DoE method depends upon several parameters especially the experimental accuracy and the measurement precision. Accordingly, the best practice before validating a MODR would be to perform confirmatory validation runs to ratify the empirical model resulting from a DoE exercise. From the regulatory perspectives, working within MODR should not be considered a change, as a method can be considered robust enough to work within this range.
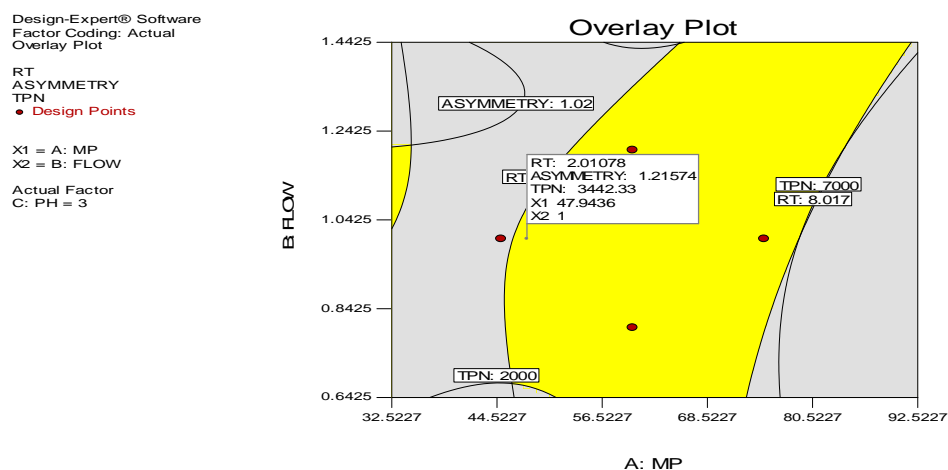

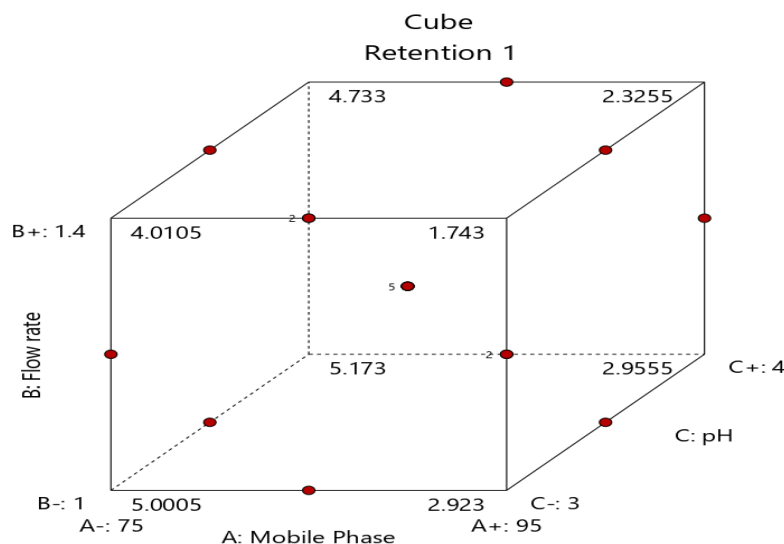**Figure No.-3: Design Space or MODR**

Figure No 4: **Analytical Design Space 3d Model: It Is The Multidimensional Combination And Interaction Of Input Variable And Process Parameters That Have Been Demonstrated.**

❖ CONTROL STRATEGY [3]

As per analytical point of view CS has been defined as the controls on input factors that ensure the method meets both traditional system- suitability criteria and wider performance- related objectives. System suitability tests are a standard part of routine application and are typically established during method validation.

❖ PROCESS ANALYTICAL TECHNOLOGY (PAT) [4]

PAT has been defined as a system for designing, analyzing, an controlling manufacturing through timely measurements (i.e, during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. The concept of PAT is complimentary to that of design space. The design space is defined by the key and critical process parameters identified from process characterization studies and their acceptable ranges. These parameters are the primary focus of on-, in-, or at-line PAT applications. In principle, real-time PAT assessments could provide the basis for continuous feedback and results in improved process robustness.

ICH Q8-Pharmaceutical Development

AQbD Approach steps:

Define Analytical Target Product Profile
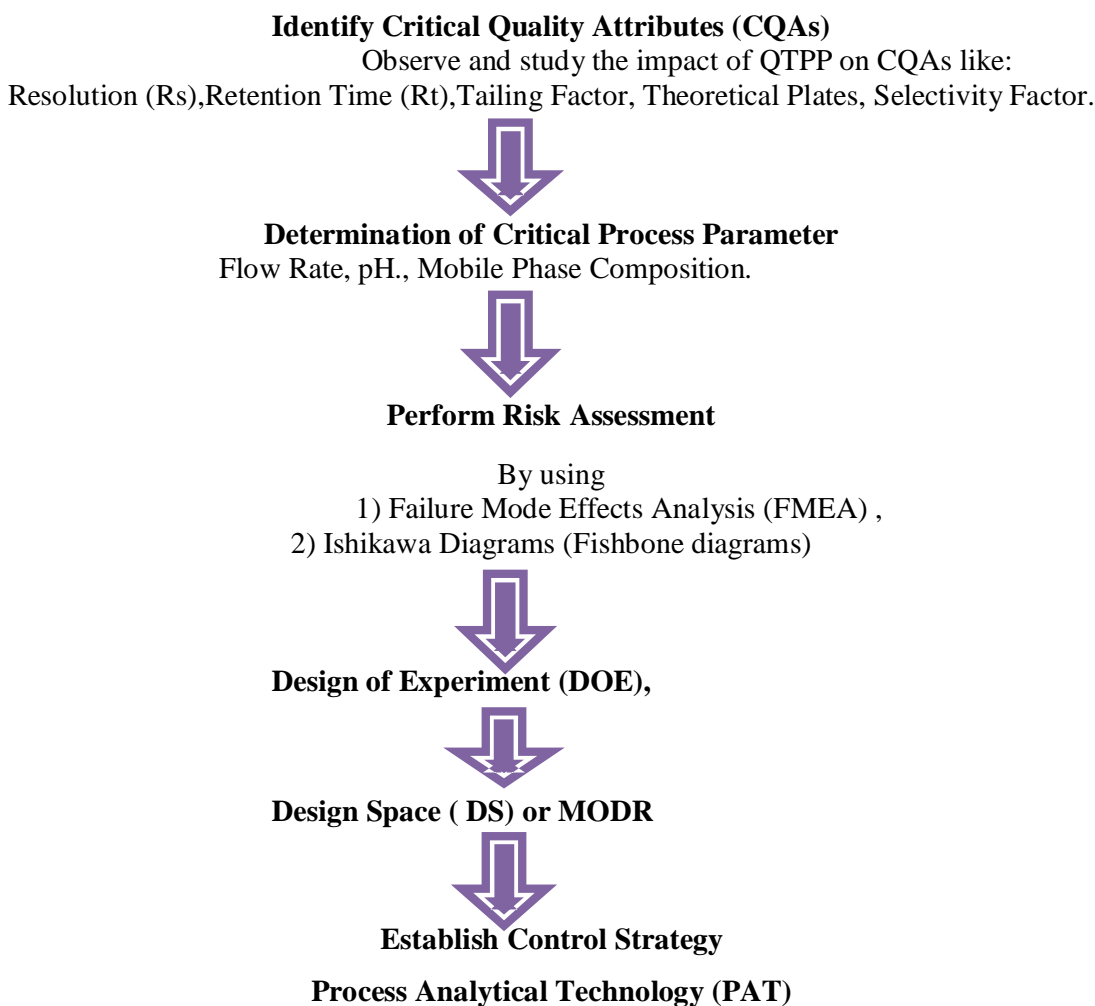Targeting the parameter: Flow Rate, Temperature, Mobile Phase Composition, pH.

Identify Critical Quality Attributes (CQAs)
Observe and study the impact of QTPP on CQAs like:
Resolution (Rs),Retention Time (Rt),Tailing Factor, Theoretical Plates, Selectivity Factor.

⬇

Determination of Critical Process Parameter
Flow Rate, pH., Mobile Phase Composition.

⬇

Perform Risk Assessment

By using
1) Failure Mode Effects Analysis (FMEA) ,
2) Ishikawa Diagrams (Fishbone diagrams)

⬇

Design of Experiment (DOE),

⬇

Design Space (DS) or MODR

⬇

Establish Control Strategy

Process Analytical Technology (PAT)

Fig No. 5:   Analytical Quality By Design (Qbd) Steps

Table No 1: Current Vs Qbd Approach To Pharmaceutical Development [1]

Current Approach	Qbd Approach
Quality assured by testing and inspection	Quality built into product & process by design, based on scientific understanding
Data intensive submission – disjoint information without "big Picture	Knowledge rich submission – showing product knowledge & process understanding
Specifications based on batch history	Specifications based on product performance requirements
"Frozen process," discouraging changes	Flexible process within design space, allowing continuous improvement
Focus on reproducibility – often avoiding or ignoring variation	Focus on robustness – understanding and controlling variation

❖ DISCUSSION

AQbD provide the basis for the deep understanding about the different steps involves in analytical method development. In simple method development the chances of method failure is more and it require repetitions of method development which increases the cost and time of method while in case method development by AQbD, it gives the robust method based on design space which is obtain after 17 trials using 3^3 Box-Behnken design.

❖ CONCLUSION

AQbD has vast importance in the pharmaceutical industries like drug development, formulation, analytical method and bioanalytical. Its play key roles in for ensuring the method reliability and non-variability in results. AQbD provide opportunity to achieve regulatory flexibility but require high degree of analytical method knowledge. In ICH Q8 & Q9 guidelines the critical analytical factors are identified which is described for process development. In ICH Q9 guideline provide identification for critical quality attributes with help of analytical target profile. Hence, all factors of AQbD together will give better knowledge for understanding method development and its improvement throughout the lifecycle. An AQbD is more efficient for future scope. By using AQbD multiple factors gives multiple results at once.

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