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A Bird's Eye View On Quality By Design (Qbd) Approach: Analytical Method Validation

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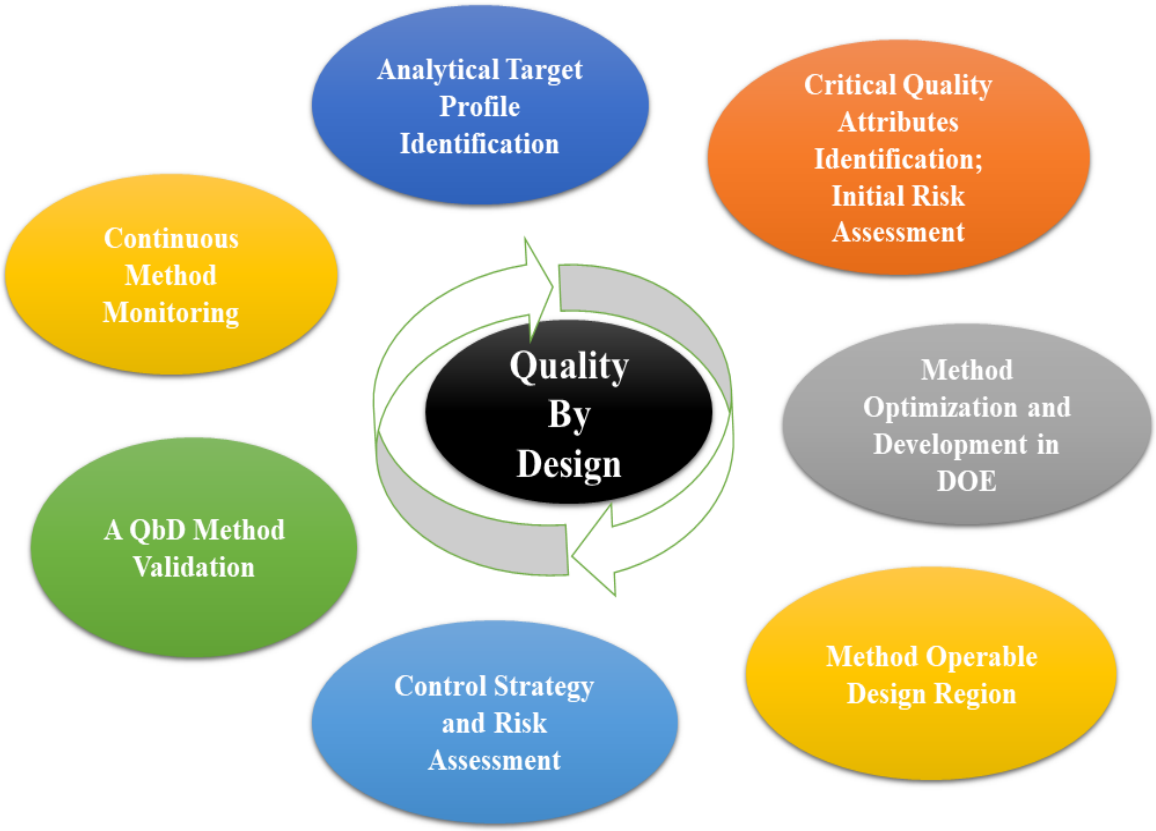
Graphical Abstract



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ABSTRACT

Quality-by-design (QbD) is a systematic approach to drug development, which commence with clear objectives. Its uses science and risk management approaches to gain product and process understanding and finally process control. The idea of QbD can be extended to analytical methods. New drug development must implement Quality by Design approach. Most of regulatory agencies and or FDA are reviewing the drug development data. To answer such agencies and FDA one has to go towards a more scientific, risk based, holistic and practical approach. The emphasis of Analytical QbD 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 outcome are recognized and subjected to methodical risk assessment employing a variety of tools and practice discussed in the article, after which the variables are optimized. The end method is validated and a control strategy is set in a position. The main objective of the present review article to describe different steps involved in method validation by QbD approach for an analytical method development and validation.

Keywords: Quality-by-design; QbD; Analytical Methods; Method Validation

1. INTRODUCTION

The pharmaceutical manufacturing is one of the main strictly regulated and governed sectors by authoritative regulatory bodies, because quality of pharmaceuticals directly related to the health of the public(1,2). Therefore there is need to control the quality of pharmaceuticals. The aim of pharmaceutical industry is to design product and manufacturing process to consistently deliver the quality product with proposed specifications (3–5).

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 of the fundamental criteria in addition to safety and efficacy for any entity to be qualified and approved as a drug(6–9). Quality is having a great importance when it is specifically related with drugs. Pharmaceutical quality can be defined as the product having the pre-specified quality attributes and regulatory specification. The concept of quality by design (QbD)has been implemented in the pharmaceutical industry through several initiatives such as the FDA's cGMP for the 21st Century and Process Analytical Technology (PAT) as well as with the regulatory documents ICH Q8, Q9 and Q10 and the FDA guidance on Process Validation(1,2,10–16).

Quality by design has become an important concept in the pharmaceutical industry for the method development and validation purpose. According to international conference on harmonization Quality by design defined as "a systematic approach to development that begins with predefined objectives, emphasize product and process that understand the process control based on scientific method and quality risk management(17). The knowledge of this may support to determine suitable and accurate process control and validation procedure. During development of analytical method and its validation, principle of quality by design can be applied as scientific manner(18–20).

ISSN PRINT 2319 1775
Online 2320-7876

Development and validation of analytical method plays a very crucial role in product development process. A robust method not only ensures the quality of drugs achieved as per the intended therapeutic use but also serves as a purity confirmation at each stage of product development life cycle (21–23). Analytical techniques broadly include estimation of physical, chemical, physicochemical and biological parameter of the substance of interest. 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 usually identified as they have various advantages over other non-chromatographic methods. These methods are versatile enough, robust, and require lesser amounts of analyte samples. With the use of automation these techniques minimize the probability of human error(24–26).

Chief element in the overall system is continuous improvement, which in turn is based 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. Fig.1 pictorially represents the building block of a QbD-based progression(27–29).

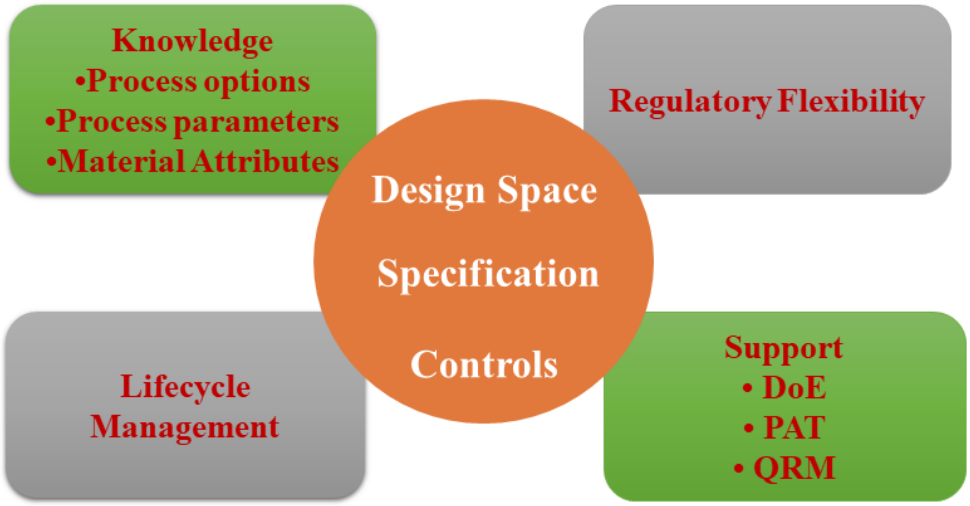

Fig. 1. Building Blocks of Quality by Design (QbD)

2. ADVANTAGES OF QbD

QbD provides flexibility in analysis of API, impurities dosage form, different stability samples and metabolites in biological sample. It also used to eliminate the batch failure along with reduction in variation in analytical attributes for improvement in method robustness(29–31).It involves most important step of pharmaceutical science i.e. product designing and process development. With the help of QbD we can do science based risk assessment which can minimize the deviations and costly investigations in product or formulation development stage(32–36).It avoids regulatory compliance problems. QbD is good science which helps in

ISSN PRINT 2319 1775
Online 2320-7876

empowerment of technical staff. It is smooth process of method transfer to the production level. QbD focuses on product safety and product efficacy(37–40).

There are many advantages of using QbD approach in analytical method development and validation procedure. It can improve the quality and integrity of product and process by means of design and scientific method(41–43). It emphasized on product knowledge and process understanding. One can set specifications based on product performance requirements. It can offers flexible and integrate process with design space, which allows continuous improvement and enhancement in the method development and validation. QbD focuses on the robustness in analytical techniques which understands the controlled variations (30,33,40,44).

3. HISTORY OF QbD

Quality by design has been seen as a new paradigm in the pharmaceutical industry, QbD is not that new. The history of QbD is represented in fig. 2(45–47).

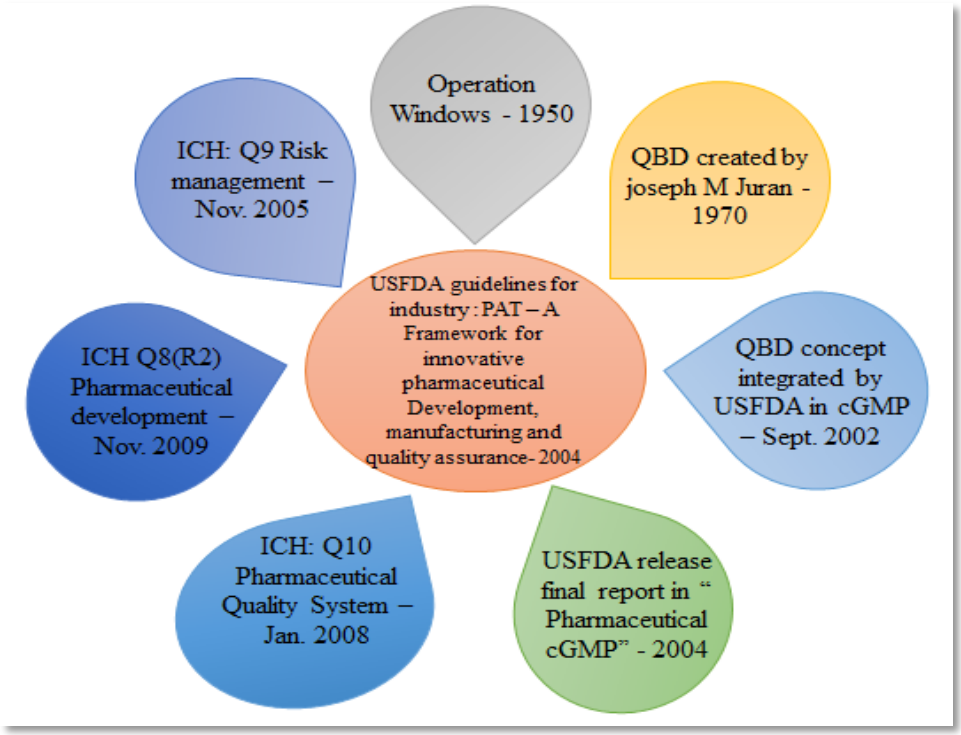

Fig. 2.The history of QbD

4. ANALYTICAL QUALITY BY DESIGN (AQbD)

Analytical quality by design (AQbD) help in to understand scientific pharmaceutical process, method, critical quality attributes and their effect on quality of product that analyzed continuous improvement till finished step of whole method. It avoids regulatory problems by reducing deviation and scientific variations, by improving the robustness(13,14). The chromatographic analytical techniques such as High performance liquid chromatography (HPLC), Gas chromatography (GC), High performance thin layer chromatography (HPTLC), super critical fluid chromatography (SFC) and liquid chromatography-Mass spectroscopy (LC-MS) are widely known as they have various advantages over non-chromatographic methods(48–50). These techniques are versatile, accurate, précised, robust, and require small

ISSN PRINT 2319 1775
Online 2320-7876

quantity of sample for analysis. With the use of these automatic techniques minimize the probability of human error(48,51,52).

4.1 Element of Analytical Quality by Design (AQbD)

1. Analytical Target Profile (ATP)
2. Critical Quality Attributes (CQA)
3. Risk Management (RM)
4. Method Operational Design Region (MODR)
5. Control Strategy (CS)
6. Life Cycle Management (LCM)

Tools of QbD

1. Design of Experiments (DOE)
2. Process Analytical Technology (PAT)
3. Risk Management Technology

Step 1: Analytical target profile (ATP)

AQbD is beginning with an analytical target profile. Analytical target profile defined as the aim of the analytical method development process, relating the result of the method to describe the method requirements which are expected to be the measurement. It is specify and interpret with the help of knowledge, ICH guideline and scientific reason of the analytical process. For method measurements its needed functioning level parameter, such as precision, accuracy, range, and sensitivity and acceptance criteria(49,50,53,54).The method performance parameters as per ICH guidelines Q2 (R1) are represented in table 1.

Generally, ATP for analytical procedure contains following parameters,

1. Selection of target analytic (API and impurities, pharmaceutical products)
2. Selection of analytical technique like HPLC, HPTLC, GC, ion chromatography and many others as per requirement.
3. Method requirements (Assay and Impurity profile)(18,22,23).

Table 1: The method performance parameters as per ICH guidelines Q2 (R1)

Performance Character	Definitions	Acceptance criteria
Accuracy	The closeness of the results obtained to the true value	90-110%
Specificity	The ability to assess unequivocally the analyte in the presence of other components that may be expected to be present	No interference with main peak
Linearity	Ability to elicit test results that are directly or by well define mathematical transformation proportional to the concentration of an analyte in the sample within a given range	Less than 0.999
Precision	The degree of agreement among individual test results	Inherent random variability

ISSN PRINT 2319 1775
Online 2320-7876

Range	The interval between upper and lower levels of analyte that have been Demonstrated to be determined with a suitable level of precision, accuracy, and linearity	NA
Limit of detection (LOD)	Characteristics of the limit test: the lowest amount of analyte in the sample can be detected	Inherent random variability
Limit of quantitation (LOQ)	The lowest amount of analyte in a sample that can be determined with acceptable precision and accuracy	Inherent random variability
Robustness	Capacity to remain unaffected by small but deliberate variations in procedural parameters listed in the procedure documentation and provide an indication of its suitability during normal range	NA

Step 2: Critical Quality Attributes (CQA)

In this step, the analyst has to identify the critical method parameters that directly effects on the performance of method. It will differ from project to project. Critical method parameters are divided into three categories such as parameter regarding analyte, parameter regarding instrument and parameters regarding operational conditions. For chromatographic experimentation sampling, sample preparation, standards, reagents, column chemistry, mobile phase composition, pH and flow of mobile phase, column temperature, detector selection, resolution, retention time, tailing factor, detection limit, threshold purity, peak purity robustness and Physical and chemical properties of the drug substance and impurities such as polarity, charged functional groups, solubility, pH value, boiling point, and solution stability are consider as critical quality attributes for analytical method development process(55–59).

The CQA parameters as per analytical technique are:

1. For HPLC method - Buffer used in mobile phase, pH of mobile phase, diluent, column, column temperature, organic modifier, injection volume and detector
2. For GC method- Gas flow, gas use as a mobile phase, oven temperature, sample concentration, program, pressure, injection volume and detector
3. For TLC and HPTLC method- TLC plate, solvent system, injection concentration and volume, time taken for plate development, visualization reagent for detection and calculation related to valid and specified results.

Step 3: Risk Management or Assessment (RM)

Risk assessment strategies areas specified in the ICH Q9 guideline. It is systematic process for the assessment, control, communication and review of risks to the quality across the product lifecycle. This step plays significant role to reach a confidence level that the method is reliable and accurate. According to ICH Q9, risk assessment can be done in three steps *viz.*, risk identification, risk analysis and risk evaluation(13,14,47). The traditional and AQbD approach for analytical method validation is represented in fig. 3.

ISSN PRINT 2319 1775
Online 2320-7876

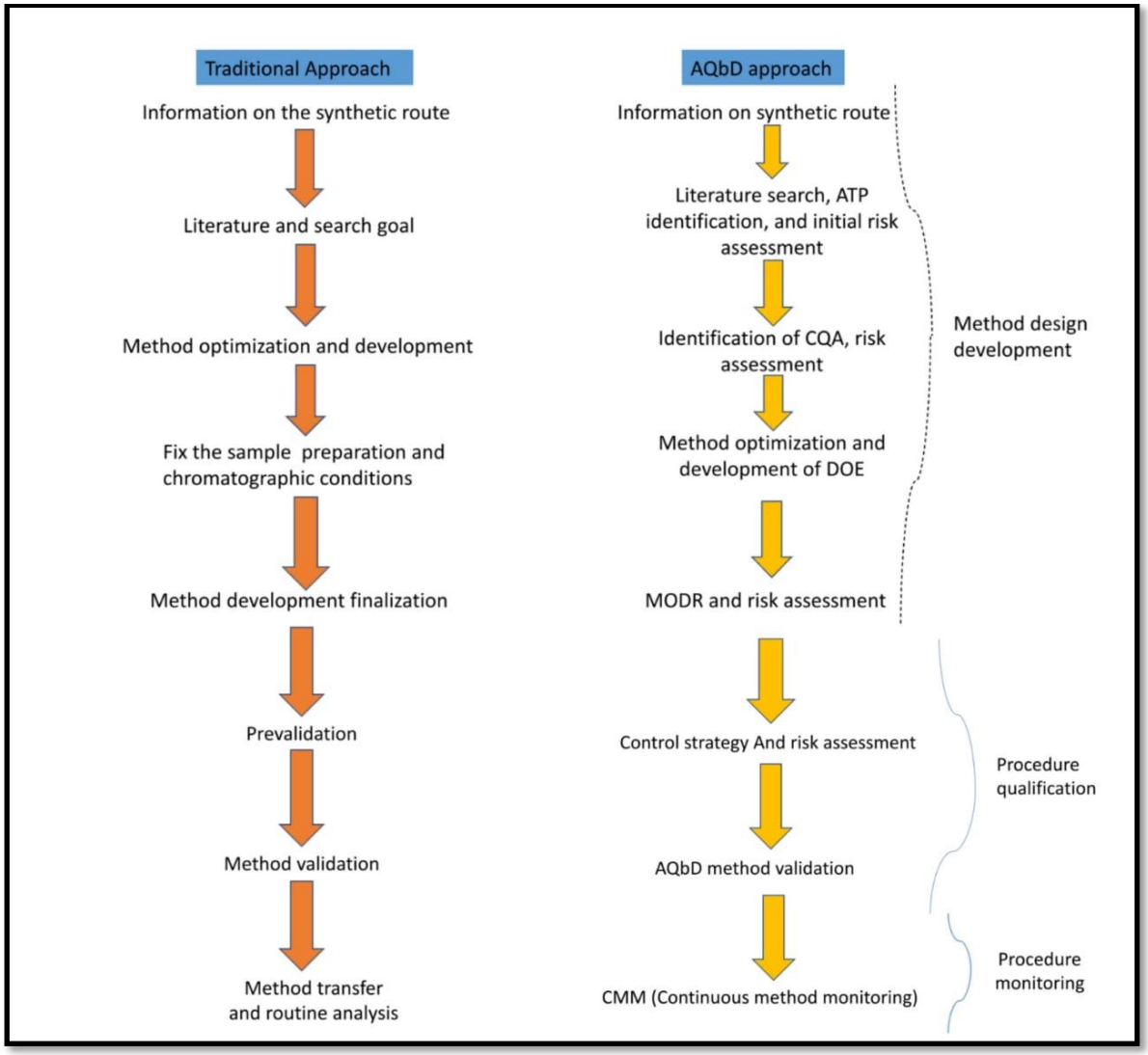

Fig. 3.The traditional and AQbD approach for analytical method validation

Risk Identification is related to identify and prioritize potential risks. These risks could be a method of instrument operation, characteristics of reagent and cycle time. It is generally advisable to determine a contingent method in case the primary method fails. In risk analysis tool like Ishikawa Fishbone Diagram and CNX approach have been used for analysis process. In CNX approach where C indicates high risk factors, N represents potential noise factors and X is the experimental factor. Risk Evaluation which is done through Failure mode and effects analysis (FMEA) and Matrix designs(55,56,58).

According to CNX approach risk factors are classified into the following categories- High Risk Factors-These are to be fixed during the method development process. E.g. sample preparation procedure; Noise Factors-These factors are subjected to robustness testing; Experimental Factors-It is related to ruggedness testing and acceptable range identification e.g. Instrumentation and operation methods(56,57,59).

Step 4: Method Operable Design Region (MODR)

MODR is a systematic chain of experiments, in which analyst able to establish the relationship between factors and their responses to evaluate all the potential factors simultaneously, systematically, scientifically and speedily. Method operable design region

ISSN PRINT 2319 1775
Online 2320-7876

(MODR) can also be established in method development phase, for serving as a source for robust and cost effective method. It is an operating range for the critical input variable, which are set out in the Analytical Target Profile. MODR permits the flexibility in various input method parameters to provide accurate method performance criteria and response before submission to FDA. Once this is defined, appropriate, the method verification and validation can be carried out. If factors are more than four, first the critical factors has to be screened out by screening designs and then optimised by optimization designs. If the number of factors is less than 4, it can be directly optimized by the optimization designs(60,61).

Selection of Designs

Screening

In screening process, qualitative variables can be screened out. It identifies various critical method parameters to be considered in the optimization experiments. For the screening process fractional factorial design and plackett burmann design can be used. If factors are more than four but less than six, then the fractional factorial design could prefer and when the factors are more than six then plackett burmann design can be used(62,63). The sequences of steps involved in risk assessment and various tools involved in the process as mentioned in ICH Q9 guidelines are represented in fig. 4.

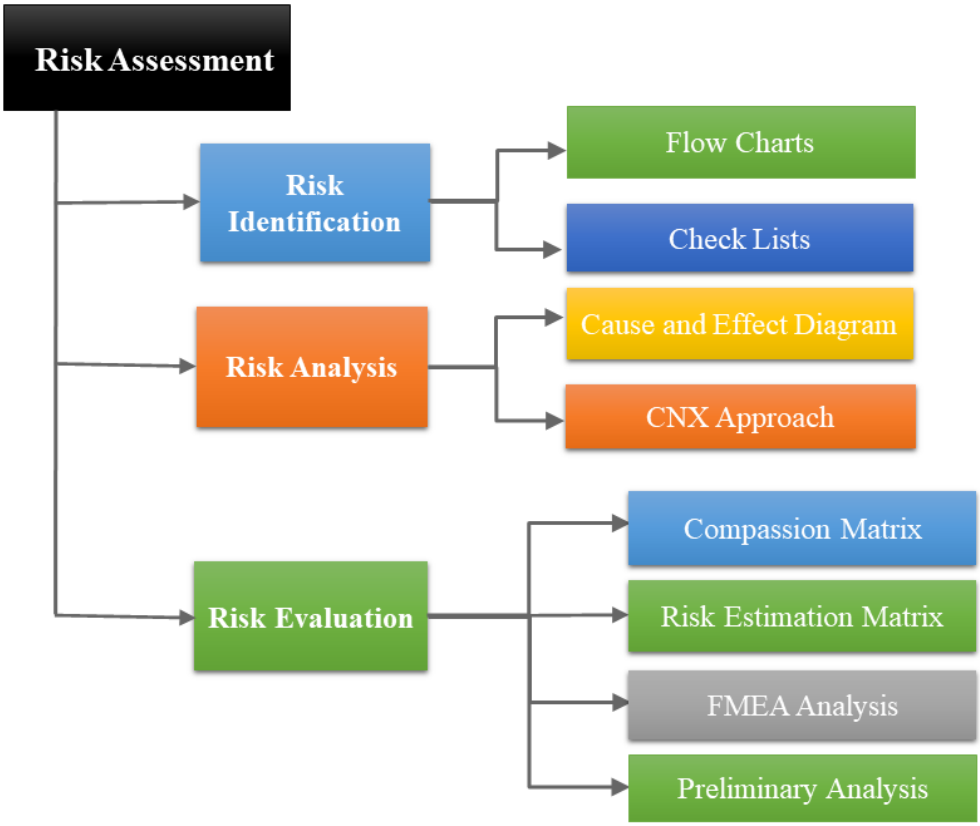

Fig. 4.The sequences of steps involved in risk assessment and various tools involved in the process as mentioned in ICH Q9 guidelines

Optimization

For optimization we can select, factorial designs, response surface and mixture designs. The main goal of optimization is to evaluate the effects and their interactions between the factors. If factors are more than two and less than five, then factorial designs can be selected. When

ISSN PRINT 2319 1775
Online 2320-7876

the factors are limited to two to four, then response surface designs are selected. When the goal of optimization related to combination of critical component and factors 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 are measured for all experimental runs for different combination of factors to be studied. After evaluation of model, all the responses should be specified for numerical and graphical optimization of all the factors(64–67).

Selection of model

After all experimental runs, model of analysis is mathematical relationship between factors and response should be selected which depends on the shape of the expected response behaviour. It could be linear, quadratic, cubic and Schaffer. For selection of Model, analysis of variance (ANOVA test) should be carried out. In many cases, to interpret the response result in mathematical relationship statistical methodology, calculation and formula should be applicable according to method requirements. It may vary method to method(50,68–71).

Interpretation of model graphs

Model Graphs will give clear idea about how the response will behave at different levels of factors at a time through predicted response equation with individual coefficients which includes

1. 1D interaction- It shows the linear effect of changing the level of a single factor.
2. 2D contour- It reveals effect of two independent factors on one response at a time
3. 3D surface- It reveals the effect of three or more factors and 4D cube.

After Development of Design, Minimum three Confirmatory Experimental Runs should be conducted within defined rang. Observed Results of these confirmatory runs will be compared with Predicted Results from Model Prediction equation by means of Correlation Coefficient (R) which should be not less than 0.9(72–75).

Step 5: Control Strategy (CS)

Planned set of control for all possible variation confirmed that ATP requirement would be met during analytical method transfer as well as routine use. This can be attained with continuous monitoring of system suitability parameters. Control strategy is not always a one-time exercise that is performed only during method development, but it can get changed with different stages of method lifecycle(76–79).

Step 6: Lifecycle Management (LCM)

Quality by Design (QbD) is approved protocol for a specific analytical method, method validation, verification and transfer that ensure the fitness of the method for its intended used in analysis. Combining together, this termed known as lifecycle management of analytical procedure, which starts with establishment of ATP and continues till the method, is in use. These activities mainly focus on performance qualification and acceptance criteria, e.g., precision study on the site of routine use. These performance qualifications which provide the assurance that the method is under control throughout its lifecycle(80–84).

5. QbD METHOD VALIDATION

The method validation parameters used in QbD are represented in fig 5.

ISSN PRINT 2319 1775
Online 2320-7876

Fig. 5.The list of method validation parameters used in QbD approach

QbD method validation approach is the validation of analytical method over a range of different API batches. It uses equally DoE and MODR knowledge for designing method validation for all categories of API manufacturing changes without revalidation. The approach provides the requisite ICH validation elements and information on interactions, measurement uncertainty, control strategy and continuous improvement. This approach requires lesser resources than the traditional validation approach without compromising quality. (70, 75, 82, 83).

It defines the method validation requirements. There are many measures of measurement performance (for example amount of API, activity of API and impurities) that may be used in method validation (see figure 3). There must be clear identification of the requirements for each method when organizing the validation plan. Figures 3, 4 are adapted from Q2 (R1) and identify the requirements to complete a method validation. These method validation parameters considerations for QbD are depicted in table 2.

 ISSN PRINT 2319 1775

Online 2320-7876

Table 2: The method validation parameters consideration for QbD

Parameters	Assay Characterization	Specificity	Linearity	Range	Accuracy
Definitions	Understanding of the factors that influence the mean and standard deviation/CV of the assay	To provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample	The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample	The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including the second centrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.	The accuracy of an analytical procedure expresses the closeness of agreement between the values which is accepted either as a conventional true value or an accepted reference value and the value found.
Typical Factors	Excipients, Concentrations, Assay Methods (# Dilutions)	Sample preparation method, controlled impurities or sample matrix	3-5 concentrations are typical with 3 min	Concentration	Well characterized standards with known potency etc.

Recommended Data and Analysis Procedure			For the establishment of linearity, a minimum of 5 concentrations is recommended. Other approaches should be justified. ICH Topic Q 2 (R1) Part II. Examination of residuals will indicate where the linear range has been established		Minimum of **9** determinations over a minimum of 3 concentration levels covering the specified range (e.g. 3 concentrations and 3 replicate each of the total analytical procedure). ICH Topic Q 2 (R1) Part II. 10+ determinations is even better for accuracy.
TIP	QRM, Process Mapping and FR Matrix to identify key factors in the analytical method	Assay or analytical method designed to detect the specific drug attribute	Linear fit, Ad R square, equation (slope/intercept)and residuals plots	Make sure concentrations exceed drug application ranges and refer to linearity study for range	Measure mean shift from reference standard
JMP Platform	DOE, Full Factorial, Custom Designs	Fit Model and or Fit Y by X	Fit Y by X or Fit Model, Residuals	Fit Y by X	Fit Y by X, Distribution and Graph Builder

ISSN PRINT 2319 1775
Online 2320-7876

Representative drug substances (DS) and drug product (DP) materials should be used during method validation. This Identical materials and standards will ensure the limits of detection and quantitation properly calculated and validated and would be performing well when measuring and testing actual product. Maturity of the DS/DP is also a consideration. Conduct all method validation tests with the correct sample size and sampling method as defined in the method SOP. Achieve acceptable results for method validation of all analytical methods. Make sure acceptance criteria have been defined for each validation method variable, modify/improve aspects of the assay so it will pass the validation testing criteria. Finally, it is necessary to determine whether the analytical method is fit for use and ready to transfer to other internal organizations or to external CRO/CMOs. This is determined by meeting all acceptance criteria for precision, bias, linearity etc. Equivalence tests are typically used for method transfer(8,10,13,20,24,85–87).

CONCLUSION

The pharmaceutical industry and its regulators are strongly focused on all quality issues because, at the end of the day, drugs often make the difference between life and death. Quality by design is an important part of the systematic approach to pharmaceutical quality. Quality by design is an understanding which is based on ICH Q8, Q9 and Q10 concepts. The Quality by design (QbD) is a best approach to encourage and support quality and to increase the further thinking about the best ways. Analytical method development and validation by QbD plays a key role in the pharmaceutical industry for ensuring the product quality. The outcome of a QbD is the understanding from product development to commercial production. It can be concluded that Quality by Design (QbD) aspect plays significant role in process understanding and create opportunities for identification of risk and developing control strategy in the formulation and process development.

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