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Quality By Design: A Systematic Approach for the Analytical Method Validation

Bhupendra Singh[1], Nisha Kumari*[2], Geetanjali Saini[1], Amit Chaudhary[2], Kritika Verma[2] Manish Vyas[3]

[1] Abhilashi College of Pharmacy, Ner Chowk, Mandi H.P., India

[2] School of Pharmacy, Abhilashi University, Mandi H.P., India

[3]Lovely Professional University, Phagwara, P.B., India

ABSTRACT

The scientific way to develop an easy and robust analytical technique for critical analysis is a QbD approach. QbD is a systematic approach to product or method development that begins with predefined objectives and uses science and risk management approaches to achieve product and method understanding and ultimately method control. The aim of the analytical QbD is to achieve quality in measurement. The main objective of this review to explain different steps involved in method development by the QbD approach for analytical method development and describes the implementation of QbD in analytical procedure validation. The advantages of applying QbD principles to analytical technique include discovering and minimizing the source of variability that may lead to poor method robustness and ensuring that the method meets its intended performance need throughout the product and method lifecycle.

Keywords: Quality by design (QbD), Risk Analysis, Analytical method validation

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***Address for Correspondence:**

Ms. Nisha Kumari, School of Pharmacy, Abhilashi University, Mandi H.P., India

Introduction

The concept of Quality by Design (QbD) was first developed by Dr. Joseph M. Juran in various publications, he called that quality could be planned. ICH Q8 guidelines were mentioned the concept of QbD, which state that "Quality should be built into the product by design but quality cannot be tested in the product". Quality is the suitability of either a drug substance or a drug for its intended uses. This term includes such attributes as the identity, purity, and strength. According to ICH Q8 (R1) Quality by design is "a systematic approach to development that begins with a predefined objective and emphasizes product and process understanding and process control, based on sound science and quality risk management".To achieve the quality in measurement is the main purpose of analytical of QbD.[1] Benefits of implementing AQbD is through an understanding of attributes of method. Enhanced knowledge sharing, development of the high-performance method, dynamic control strategy leads to greater efficient regulatory oversight, operative elasticity, regulatory filing based on science and automatic rational, improve timing to reach the market, reduce consumer-generic agnosticism, fantabulous return on investment, limited product rejects and reduce post-approval change. Analytical methods are a fundamental part of the control strategy in the pharmaceutical quality system (ICH Q10). It includes many parameters and attributes related to drug substance and drug products i.e. instrument operating condition and their associated method.[2]

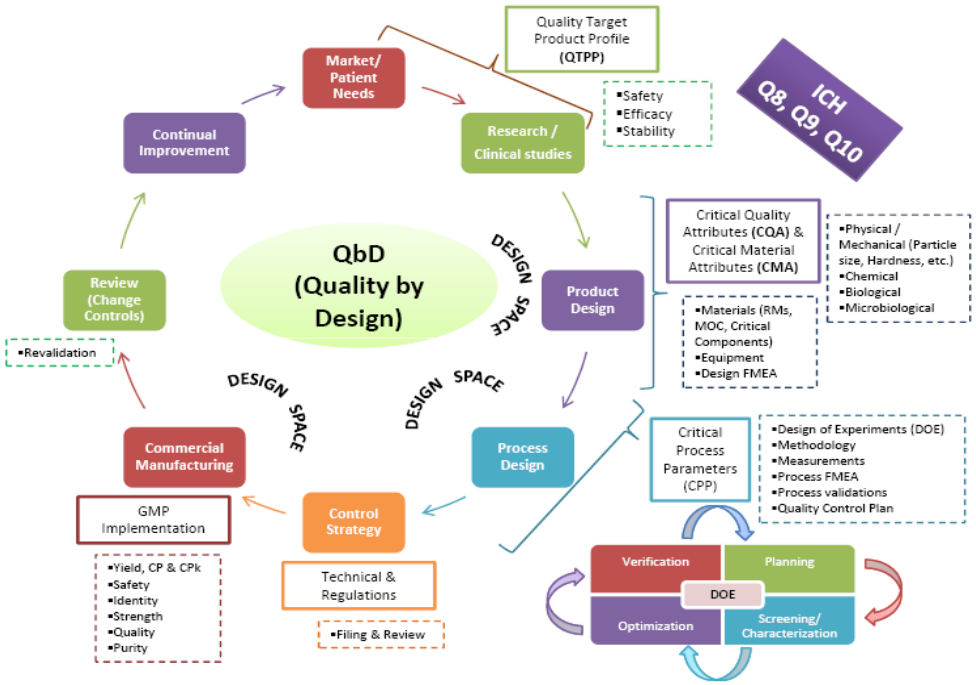

Fig 1: The Life cycle of quality by design approach (QbD)

Advantages of QbD:

- It provides better flexibility in decision making.
- It increases opportunities for life cycle approval.
- Reduce batch failure.
- It helps design for unmet medical need.
- Better knowledge of the process.
- Better quality of the review.
- It allows for continuous improvement until the end step of the method.
- Reduce deviation and costly investigation.
- It affects product design and process development.
- Reducing variability in the analytical attribute for improving the method robustness.[3]

Table 1: Difference between conventional approaches and QbD approaches.

Parameters	Conventional approaches	QbD approaches
Approaches	Based on empirical approaches	Based on systematic approaches
Quality	Quality assurance including final product testing and inspection.	Quality is maintained throughout the method development phase
Method	Fix, change cannot support	Flexible, it allows continues improvement
Reliability	Based on batch trial and validation report	Based on method performance to ATP criteria
Submission	Submission only data	Submission with product designing and knowledge
Cost	If any change to occur in the process involve hug lose in cost	Cost effective method

Analytical method development strategies: [4]

The main application of quality by design (QbD) principles for development of analytical method is focused on the principle of building quality into the analytical method during its development. Because of this, the actual method development process for an analytical quality by design (QbD) method should follow a structured approach. The aim of the QbD method development is comply with predefined objectives. The objective of the QbD method development can be illustrated using HPLC an example. The aim of the HPLC method for API is generally to separate and quantify the main compound and the critical quality attributes (CQA0) that may impact the quality of the drug product. The specifications should meet regulatory requirements such as specificity, linearity, accuracy, precision, robustness and ruggedness.

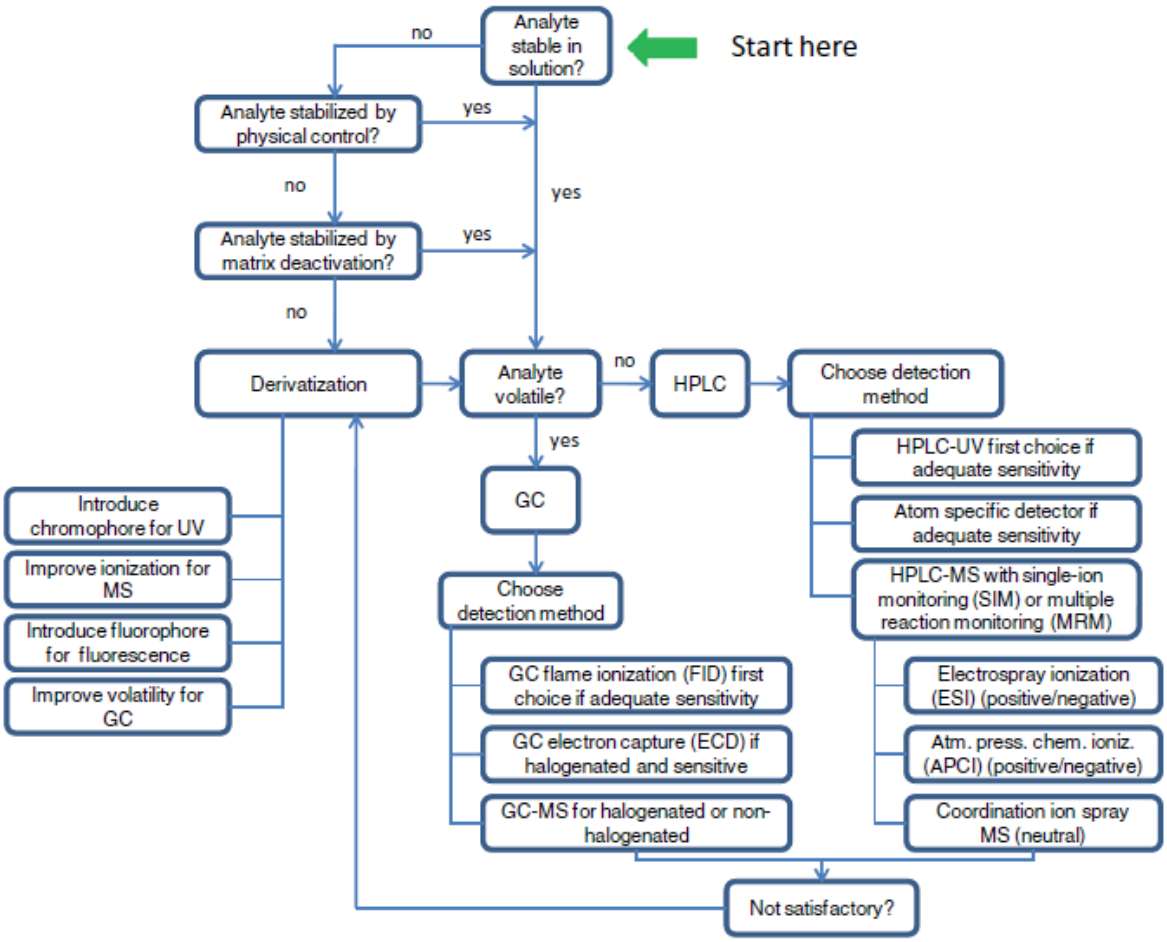

Fig 2: A schematic representation of method development strategies for analysis of impurity through different analytical techniques [4]

Steps of QbD approach in analytical method development:

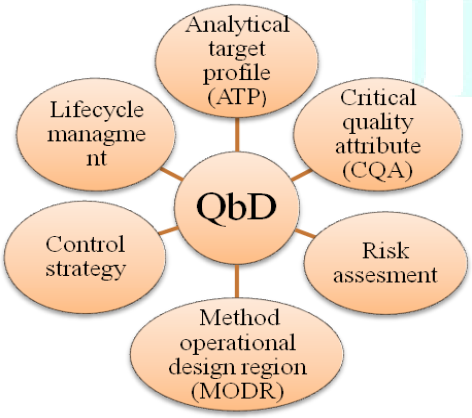

Fig.3: Different steps of quality by design QbD

1. Analytical target profile (ATP):

QbD is beginning with an analytical target profile, which is a linear to QTPP. Analytical target profile defines the aim of the analytical method development process, relating the results of the method to attain QTPP. ATP describes the method requirements which are expected to be the measurement. The analytical target profile is specifying with the help of knowledge and scientific reason of the analytical process. The ATP defines to what level the measurement is needed (i.e. functioning level characteristics, such as precision, accuracy, range, and sensitivity) and what the method has to measure (i.e. acceptance criteria). [5]

Generally, ATP for analytical procedure contains a selection of target analytic (API and impurities), selection of analytical technique (HPLC, HPTLC, gas chromatography, ion chromatography, etc.) and method requirements (assay and impurity profile).

Table 2: Method performance characteristics as per ICH Q2 (R1) & USP [6-7]

Performance characteristics	Definition	Categorization
Accuracy	The closeness of the results obtained to the true value	Systematic variability
Specificity	The ability to assess unequivocally the analyte in the presence of other components that may be expected to be present	
Linearity	Ability to elicit test results that are directly or by well defined mathematical transformation, proportional to the concentration of an analyte in the sample within a given range	
Precision	The degree of agreement among individual test results	Inherent random variability
Limit of detection (LOD)	Characteristics of the limit test: the lowest amount of analyte in the sample can be detected	
Limit of quantitation (LOQ)	The lowest amount of analyte in a sample that can be determined with acceptable precision and accuracy	
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	N/A
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	N/A

2. Critical quality attributes (CQA):

CQA is the second step of QbD. According to ICH Q8, CQA is defined as a physical, chemical, biological property that should be within an appropriate limit, range to ensure the desired product quality. (8)CQA for analytical method consists of method parameters and method attributes. The analytical technique of CQA can differ from one to another.

- CQA for the GC method is the temperature of the oven and its program, injection temperature, gas flow rate, sample diluents, and concentration.
- CQA for the HPLC method is mobile phase buffer, pH of the mobile phase, column selection, organic modifier, and elution method.
- CQA for HPTLC method is TLC plats, mobile phase, Injection concentration and volume, time taken for plate development, a reagent for color development and detection. [8-9]

3. Risk assessment:

When CQA has been studied, the next step is to describe the relevant risk assessment. Once the technique is identified, analytical QbD focuses on the assessment of the risk associated with variability includes analyst method, instrument configuration, measurement and method parameters, sample characteristics, Sample preparations, and environmental conditions. [10]

According to ICH Q9 guidelines, risk assessment is a systematic process for the assessment, control, communication and review of risk to the quality across the product lifecycle. Risk identification, risk analysis, and risk evaluation are the three-step of risk assessment. [11]

Fig 4: Different steps of risk assessment.

The first step of risk assessment is very important to identify and prioritize potential risk. These risks include methods of operation of the instrument, characteristics of reagent and cycle time. It is the most desirable to determine a contingent method in case the primary method fails. Flow chart and check list are used to describe the risk factor.

The second step of risk assessment is risk evaluation. Fishbone diagram is used to perform risk assessment, also called Ishikawa. According to this approaches the risk factor is divided into three categories- high-risk factor, noise factor and experimental factor. [12]

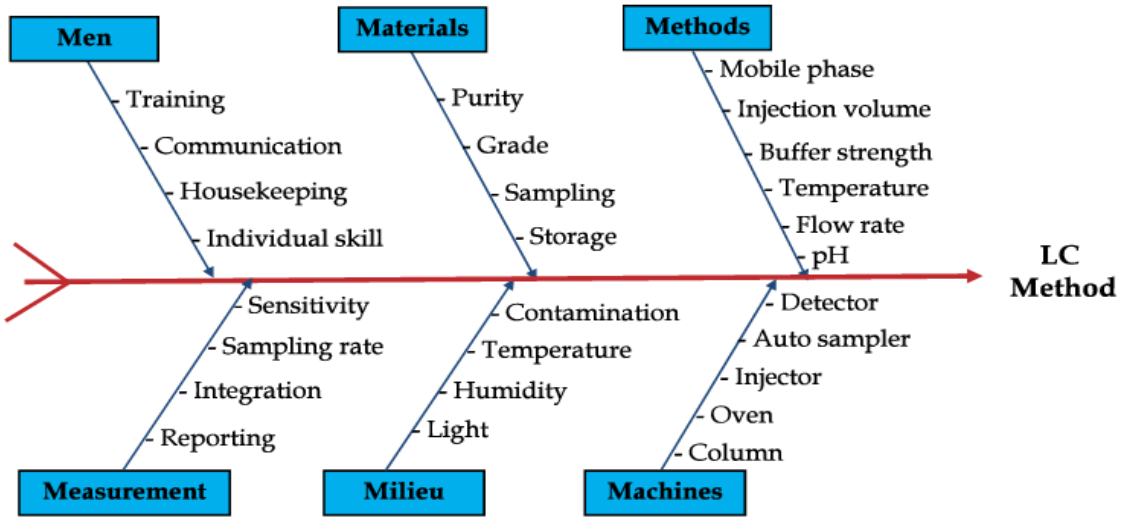

Fig 4: Ishikawa cause-and-effect fish-bone diagram for a liquid chromatographic method development

The highest identified risk related to the stability of the sample and standard. Stability of the samples and standards to be evaluated and also to be focused on the level of related substances in standard and samples. The sample or standard may absorb the water during weighing which could be considered as the second highest identified risk

.

Table 3: Risk assessment and control strategy [13]

Potential failure cause	Failure effect	Risk mitigation	P	S	D	Total
Water source	Change the peak resolutions S/N	Compare mobile phase from each lab during precision testing	2	1	1	2
Sample stability	Changes in peak resolutions S/N	ascertain the stability of prepared sample solutions during the validation study	2	1	2	2
Standard	Changes in the standard potency and purity	ascertain the stability of prepared standard solutions during the validation study	1	4	5	20
Mobile phase stability	Changes to chromatography	Establish the stability of prepared samples/solutions during the validation study	2	1	2	2
Columns	Lot variability may change in peak resolutions S/N	Evaluate at least two different loads	2	1	1	2
Reagents	Lot variability may change in peak resolutions S/N	Perform evaluation during the study	3	1	1	3
Vials	Exposure to light results in an increase of impurity	Amber vials to be used. Use same vials for standard and reference	1	3	1	3
Humidity	Humidity changes in the laboratory may result in accurate weighing	Standard operating procedures to be followed to dry the samples and standard	1	4	3	12
Column temperature	Changes in the laboratory temperature may change the peak resolutions S/N	Study and control column temperature if required	3	1	1	3
Sample temperature	May change the peak resolutions S/N	Study and control autosampler temperature if required	3	1	3	3
Sample/standard light exposure	May cause changes in the purity of sample/standards	Use amber vials and use the same conditions for sample and standards	2	3	1	6
Sampling rate	May cause changes in the purity and potency values	Control in HPC within the specified range	1	1	1	1
Misidentification of peaks	Incorrect values reported for known impurities	Training, example chromatograph	4	2	1	8
Instrument model	Changes to peak resolution S/N	Previous studies obtained acceptable LOQ on two HPLC/UV model	1	1	1	1

S/N= Signal to noise, P=Probability, S=Sevierity, D=Detectability

The risk assigned to each failure modes was calculated as Risk= Severity X Probability X Delectability and calculated as risk priority number (RPN)

4. Method operational design region:

Once method development and risk assessment have been identified the next step is method operational design region. MODR is used to method development operational region for daily operation. MODR is based on science, risk-based and multivariate approach to measuring the effect of various factors on method performance. It is also used to set up important method control such as system suitability, RRT and RRF. [14]

5. Control strategy:

The control strategy is the control design set. It is calculated from the analyst nature and MODR understanding. The method control strategy can be set up on complete statistical data collected during the MODR. The control strategy is not forever a onetime practice that is performed during the method development phase but it can get changes with different phases of the method lifecycle. It is noted that the method control strategy of QbD approaches does not differ from conventional approaches. [15]

6. Lifecycle management:

Lifecycle management is the last step of QbD. It is a continues process of sharing knowledge gain during the method development phase includes the final result of risk assessment, assumption based anterior knowledge, MODR, control strategy CQA and analytical target profile. The lifecycle management of QbD approaches different from conventional approaches.

7. Experimental design

The experimental design is a statistical approach to systematize the experiments so that the requisite information is obtained precisely and efficiently, before the conduct of experimental studies. Prior to the selection of an apt experimental design, it is important to demarcate the experimental domain or region of interest within a factor space. [16]

7.1 Design of experiments:

The process of determining the most suited composition and operating conditions is called optimization. The term optimizes literally means to bring something as close to perfection as possible. A number of variables are involved in the design and development of pharmaceuticals. The variables that can be controlled by the manufacturer are called independent variables/factors and these independent variables have the potential to influence the characteristics of the analytical method and outputs. Levels are the values of the factors. The properties exhibited by finished products are termed as response variables or dependent variables. Any change in independent variables leads to a corresponding change in the dependent variables. [17]

The different types of Design of Experiments (DoE) optimization methodologies have been illustrated in **Figure 4.** DoE has evolved into a powerful tool that elegantly provides a large number of information with the least runs

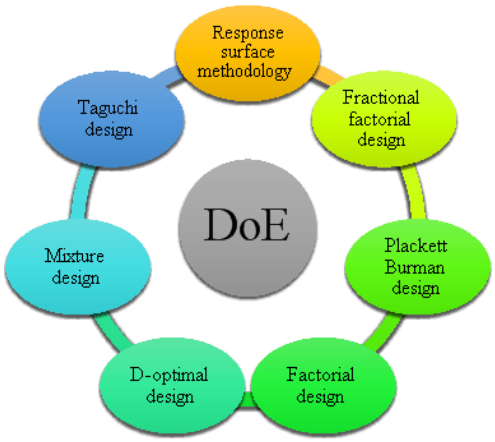

Fig 5: Design of experiments (DoE) optimization methodologies

Table 4: Quality by design vital terminology

Term	Definition
Optimize	Make as perfect, effective, or functional as possible
Optimized	Improved product to accomplish the objectives of a development scientist using DoE and computers
Optimization	Implementation of systematic approaches to achieving "the best" combination of product and/or process characteristics under a given set of conditions
Independent Variables	Input variables, which are directly under the control of the product development scientist
Quantitative Variables	Variables that can take numeric values
Categorical Variables	Qualitative variables which can not be quantified
Runs or Trials	Experiments conducted according to the selected experimental design
Factors	Independent variables, which influence the product/process characteristics or output of the process
Design Matrix	The layout of experimental runs in matrix form, as per experimental design
Knowledge Space	Scientific elements to be considered and explored on the basis of previous knowledge as product attributes and process parameters
Design Space	Multidimensional combination and interaction of input variables and process parameters demonstrated to provide quality assurance
Control Space	The domain of design space selected for the detailed study
Critical Quality Attributes (CQA)	Parameters ranging within appropriate limits, which ensure the desired product quality

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Authors Contributions

All the author have contributed equally

Conflict of Interests

None declared

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