Review Article

A Review: Analytical method development using QbD Tools

Rekha Bhalerao[1], Ashish Phuge[1], Vijaya Barge[2*]
Research Scholar[1], Associate Professor[2] , Department of Pharmaceutical Chemistry [2]
[1]PDEA's Seth Govind Raghunath Sable College of Pharmacy, Saswad, Pune - 412301, Maharashtra, India.
[2]PDEA'S Shankarrao Ursal College of Pharmaceutical Sciences & Research Center, Kharadi, Pune -14, Maharashtra, India.

Corresponding Author:
Vijaya Barge
E-mail: godse _vijaya@rediffmail.com

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Abstract:

In a QbD approach, the impact and interactions between critical method variables are understood using a Design of Experiments approach. QbD tools such as risk assessment and design of experiments incorporate better quality into the analytical method, facilitate prior understanding and identification of variables affecting method performance. The main objective of the present review article to describe different tools involved in method development by QbD approach for an analytical method development. The objective of this review article is to provide a brief idea about quality risk management, Analytical Target Profile, Design of Experiment in method development.

Key Words: Quality by Design, Design of Experiments, risk assessment

Introduction:

Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives, emphasizes product understanding, process understanding, process control, based on sound science and quality risk management which has the aim of improving product quality and increasing regulatory flexibility.

It is an important tool for the development of precise, accurate and robust analytical method. Using QbD, quality is embedded into the process from the beginning to the end of the process, which counteracting the traditional approach, thus we get the quality method at the end of the process. analytical target profiles (ATPs) and operational design ranges for analytical methods are defined using QbD tools like Experimental design and risk assessment.[1-4]

Risk management and various terminologies associated with it, like Risk Acceptance, Risk Analysis, Risk Assessment, Risk Communica- tion, Risk Control, Risk Evaluation, Risk Identification, and Risk Management have been well described in ICH guideline Q9.[5,6]

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 guidelines ICH Q8, Q9 and Q10 and the FDA guidance on Process Validation.[7] The design space reffered as manufacturing area of the product including Equipment, Material, and Operators and Manufacturing Conditions.

International Conference on Harmonisation (ICH) guidelines given for pharmaceutical development that begins with predefined objectives and emphasizes product and process control based on quality risk management.

ICH guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. Different aspects of pharmaceutical quality contain development, manufacturing, distribution and the inspection and submission processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products according to ICH guideline.

Tools In QbD Approach[8]

Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools used in the QbD process. Prior knowledge of these tools is valuable to facilitate QbD implementation. A successful product/process development strategy requires thorough understanding of QbD principles and the tools for establishing the QbD strategy. Risk-based product or process development strategy is carried out with the help of QbD. Design of experiments, risk assessment and PAT are the most commonly Used tools for the establishment of QbD principles. Design space are established by QbD provides an opportunity for flexibility in constructing a more meaningful design space. The changes in product and process development can be managed in a better way with QbD.

Quality Risk Management Process

Quality risk management is defined as systematic approach for the assessment, control, communication and review of risks to the quality of the drug product across its lifecycle. It is always not possible to use a formal risk management process using tools and standard operating procedures. It is a better way to use informal risk management processes using empirical tools and procedures.

Quality:

The comparision of set of inherent properties of a product, system or process with a standard given in ICH guideline, for "quality" of drug substance and drug products we follow Q6A guideline.[9]

Quality risk management:

A Quality Management is defined as inbuilt the quality in product by a systematic way using process assessment, control, communication and review of risks to the quality of the product across the product lifecycle.

Quality system:

For the implementation of quality in product quality policy and quality objectives are given in guidelines called Quality system.

Risk:

Risk mainly reffered as Probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).[10]

Risk acceptance:

Depend upon risk severity it is decided to accept risk called risk acceptance. (ISO Guide 73). Risk is mainly characterized by potential events and consequences or a combination of event.[11]

Risk analysis:

To determine which type of risk observed and estimation of the severity of risk is called risk analysis. It is mainly associated with the identified hazards.

Risk assessment:

For analytical QbD process risk assessment plays an important role. It is a systematic process for identification of hazards and evaluation of risks associated with exposure to those hazards.

Risk control:

For management of risk, implementation has been done called as risk control. (ISO Guide 73).[11]

Risk evaluation:

Risk evaluation involves comparison of estimated risk to given risk using a quantitative or qualitative scale to determine the significance of the risk.

Risk identification:

The systematic way for identification of risk using the information and referring different risk question or problem description.

Risk management:

Risk management involves systematic use of quality management policies, procedures for controlling, communicating, reviewing the risk.

Risk review:

Monitoring the results observed during risk management process called as risk review which is helpful for new knowledge.

Principles Of Quality Risk Management

principles of quality risk management are:

- The evaluation of the risk to quality based on scientific knowledge and
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.
- Quality development, business develop- ment, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical department are the responsibilities of risk management

Methods of risk assessment: Some methods of risk assessment are mentioned in ICH guideline Q9 as follows:

- Failure Mode Effects Analysis (FMEA);
- Failure Mode,
- Effects and - Criticality Analysi (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools. Analytical Method performance:[12]

Method performance is comprised of systematic (bias) and random (variance) components. A categorization of the analytical method performance characteristics in terms of systematic and random components is shown in *Table 1*.

High-level categorization of the performance characteristics are accuracy, specificity, and linearity measure systematic deviation from the reference value, and precision, detection and quantification limits are inherent measures of random dispersion.

Among these performance characteristics, accuracy and precision provide the critical information needed to quantify

an unknown amount of the substance using the method. A method cannot be accurate and precise without adequate specificity, linearity over a stated range, sufficient peak resolution for accurate integration, repeatability of injections, etc. These are important characteristics to evaluate during method development and provide an extensive data set for setting method controls as they lead to an accurate and precise method.

Range is an important component that is established based on acceptable behavior of both systematic and random performance characteristics and robustness defines an operational range of method factors, procedural parameters.

Table 1. : Types of method Performance Characteristics and its categorization

Sr. No.	Performance Charecteristics	Definition	Categorization
1	Accuracy	Closeness of result to true value	Systematic variability (bias)
2	Specificity	Ability to assess unequivocally the analyte in the presence of other components that may be expected to be present	
3	Linearity	Ability to elicit test results that directly or by well-defined mathematical transformation, proportional to the concentration of analyte in samples within the given range	
4	Precision	The degree of agreement among individual test results	Inherent Random Variability
5	Detection limit	The lowest amount of analyte in a sample that can be detected	
6	Quantification limit	Lowest amount of analyte in a sample can be determi9ned with acceptable precision and accuracy	
7	Range	The interval between upper and lower levels of analyte to be determined with a suitable level of Precision, Accuracy and Linearity.	Not Applicable
8	Robustness	Capacity to remain unaffected by small but deliberate variations in procedural parameters and provides an indication of its suitability during normal usage.	

Analytical Target Profile (ATP)[13,14]

The Analytical Target Profile (ATP) is a analytical method performance requirements, and should incorporate a joint criterion for accuracy and precision in order to define method acceptability in terms of the uncertainty of results generated by the method. Other meth\d performance characteristics (linearity, specificity, etc.) do not need to be incorporated in the ATP.

as they are not directly linked with measurement of true value.

Analytical Target Profile for analytical method development:

The procedure for analytical target Profile involve[15,16]

a. Selection of target analytes (API and impurities),
b. Technique selection (HPTLC, GC, HPLC, Ion Chromatography, chiral HPLC, etc.),
c. Choice of method requirements:

Method requirements can differ from one method to another. Based upon analytes nature suitable analytical technique can be selected.

Analytical techniques includes the following..

1. identification by IR: FTIR spectrophotometer, 2.impurity profile (Chromophore): HPLC with UVdetector,
3. impurity profile (nonChromophore): HPLC with RID/ELSD
4. Assay by HPLC (Chromophore): HPLC with UVdetector,
5. Assay by HPLC (nonChromophore): HPLC with RID/ELSD

Design of Experiments:[17]

To study the design of experiment it is necessary to consider the risk assessment. A Determination of relationship between factors affecting a process and the output of that process in an

organised way is known as "Design of Experiments" (DoE). DoE is an excellent tool that allows systematically manipulation of factors according to a pre-specified design. A doE study gives better understanding between product and process. DoE is method to determine the relationship between the inputs and outputs of a process. It also help to identify optimal conditions for analytical method. It is wise to establish a Design Space through Design of Experiment for multivariate experiments. Acoording to ICH Q8 Design Space is the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality.

Advantages of QbD :

1. Development of a robust method for analysis.
2. Variability parameters can be better controlled.
3. Method Transfer success is greater when method is transferred from research level to quality control department.
4. It provides a space for invention of new techniques by continuous improvement throughout life cycle.
5. Enhanced understanding of the knowledge space.

Limitations of QbD

1. Lack of Complete understanding of AQbD
2. Need to study MODR (Method Operable Design Region), ATP, analytical method control strategy and method performance criteria and other e lements of AQbD
3. Additional guidelines need to be developed for implementation of AQbD.
4. Require to learn new tools and skills.

Application of QbD approach for method development:

1. QbD can be applied for analytical methods which include Chromatography like HPLC For stability studies, method development, and impurity Profiling.
2. Hyphenated technique like LC–MS. Advanced techniques like mass spectroscopy, Ultra HPLC, and capillary electrophoresis.
3. A novel RP-HPLC method for quantification of tapentadol HCl in pharmaceutical formulations.
4. QbD approach for analytical method development of anti-psychotic drug (resperidone).
5. Quality by design (QbD) based development and validation of an HPLC method for Amiodarone hydrochloride and its impurities in the drug substance.

QbD is mostly applied for the development and evaluation of analytical methods. During method development it is necessary to study all potential factors (the inputs) and all critical analytical responses. Critical analytical factors are identified in an approach that resembles with process development given in ICH Q8 and Q9. QbD approach based on tools including design of Design of experiments (DOE), risk assessment, and process analytical technology (PAT). QbD is a cost and time efficient approach for analytical method development.

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Conflict of Interest: Nil

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