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QUALITY BY DESIGN APPROACH FOR ANALYTICAL METHOD DEVELOPMENT

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ABSTRACT

Quality by Design (QbD) is a concept first outlined by well known quality expert Joseph M. Juran and 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. A conventional method may fail to meet the intended purpose during method development and validation.In a QbD approach, the impact and interactions between critical method variables are understood using a Design of Experiments (DOE) approach, which incorporates statistical multi-variate analysis and modeling leading to consistent quality of drug product. QbD tools like risk assessment and design of experiments, enable better quality to be incorporated 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 steps involved in method development by QbD approach for an analytical method development. The QbD Approach for method development comprises of the following steps which include defining method intent, performing experimental design, evaluating experimental results and selecting final method conditions and performing risk assessment with robustness and ruggedness evaluation. The purpose of analytical QbD is to attain quality in measurement. The objective of this review article is therefore to provide a comprehensive understanding on various aspects of QbD, along with addressing the concerns related to its implementation.

KEY WORDS: *Quality by design,Critical attributes,Analytical target profile,Quality risk assessment,Design of experiments*

1.INTRODUCTION

The concept of quality by design (QbD)[1]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. The basic concept of QbD[2] is "The Quality cannot be tested into the product, but it should be built into it." The design space is defined as a manufacturing area of the product including Equipment,Material, and Operators and Manufacturing Conditions. Quality by Design(3) is the modern approach for quality of pharmaceuticals. Quality[2] is "The degree to which a set of inherent properties of a product, system or process fulfils requirements" (ICH Q9).The foundation of Quality by Design[3] is ICH Guidelines .Qualityby Design (QbD) has become an significant concept for the pharmaceutical industry that is further defined in the International Conference on Harmonisation (ICH) guidance on pharmaceutical development 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".

The outcome of using QbD concepts is a well-understood product and process that consistently delivers its intended performance. The knowledge obtained during development may support the establishment of a design space and determines suitable process controls. During development of analytical methods,same QbD principles can been applied to the development of analytical methods.

Various quality and statistical tools and methods, such as statistical designs of experiments, multivariate statistics, statistical quality control have been comprised in QbD. The main goal for changing from quality by testing (QbT) paradigm is to accelerate the understanding of the processes and products such

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that products quality, processes efficiency and regulatory flexibility can be attained. Liquid chromatography (LC) is the most commonly applied separation technique in pharmaceutical industry and High performance liquid chromatography (HPLC)[4] particularly Reversed Phase HPLC (RP HPLC), is one of the widely accepted analytical technique in the pharmaceutical industry.To accomplish the quality in HPLC methods QbD has become quite important .In HPLC methods, robustness and ruggedness should be established early in the method development stage to make certain method performance over the lifetime of the product for the implementation of QbD or else, if a non robust or non rugged method is adapted, significant time and resource may be required to redevelop, revalidate and retransfer analytical methods.

There are many tools such as ATP (Analytical Target Profile), CQA, Risk Assessment, Method Optimization and Development with DoE, MODR (method operable design region), Control Strategy and Risk Assessment, A QbD Method Validation, and Continuous Method Monitoring for QbD lifecycle.

Chemometrical tools such as design of experiments (DoE) methodology are closely related to QbD and many basic concepts are very similar. Therefore DoE methodology combined with methodologies for identification of design space provides deep understanding of analytical systems and enable the identification of experimental region where the quality will be assured. In the past, the common practice to develop an analytical method in liquid chromatography was performed by a trial and-error approach, for example by varying one-factor-at-a-time(OFAT) and examine the resolution of peaks until the best method was found. This approach was time-consuming and required a large amount of manual data interpretation. It frequently results in a non-robust performance when transferred into another lab because interactions between factors were not taken into account.

The OFAT approach can be used to understand changes in selectivity by keeping everything fixed and only varying one factor and if the factor of interest is known not to have an interactive effect with any other factor studied.

A more systematic concept uses experimental design plans as an efficient and fast tool for method development. In a full or fractional factorial design a couple of experiments are carried out in which one or more factors are changed at the same time. Using statistic tools the effect of each factor on the separation can be calculated and the data be used to find the optimum separation. Few examples are use of the Plackett–Burman design or the Monte-Carlo simulation in a multivariate data analysis software package (e.g. Fusion AE) .A very smart and computer-assisted way of developing a chromatographic method is by using software modeling packages (e.g.DryLab, ChromSword,ACD/LC simulator).

Even with small number of experiments these software applications can forecast the movement of peaks in reversed-phase liquid chromatography separations due to a changein the mobile phase composition or pH, temperature, flow rate and the column dimensions and particle size Other prevalent approaches in HPLC method development uses the molecular structure, or physicochemical properties such as logP, logD and pKa of the sample components to approximate their retention and optimal separation conditions.

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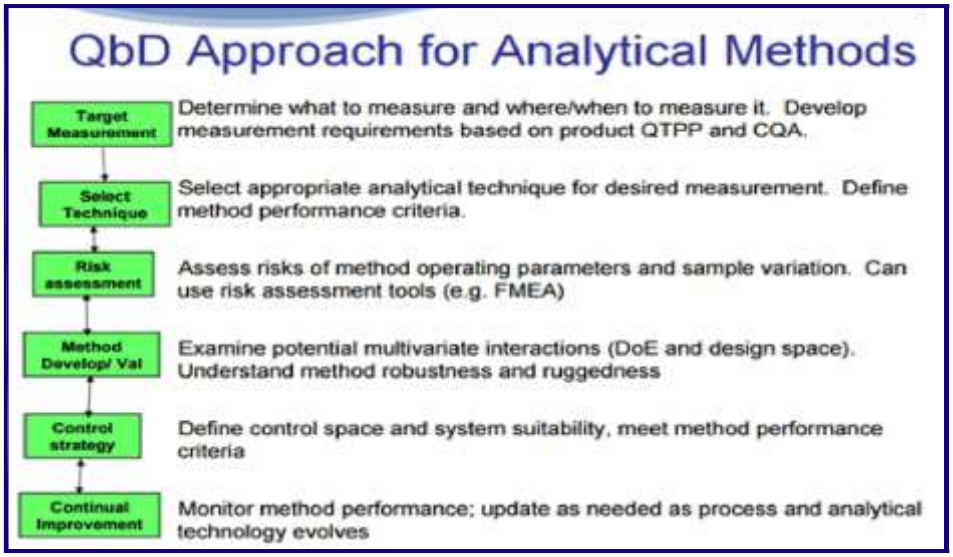
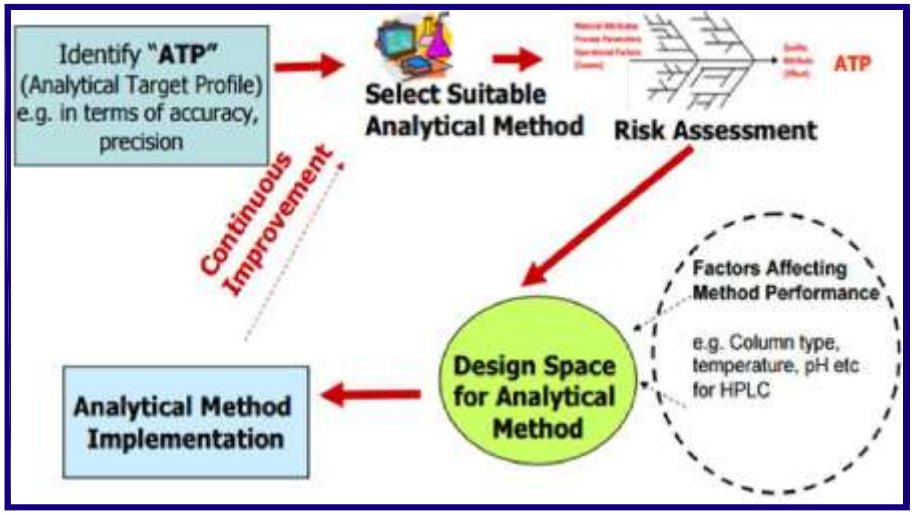


Current approach	Qbd approach
1) Quality is assured by testing and inspection	1) Quality is built into product & process by design an based on scientific understanding
2) It includes only data intensive submission which includes disjointed rmation without big picture"	2) It includes Knowledge rich submission which shows product knowledge & process
3) It focuses on reproducibility which often avoids or ignores variation	3) It focuses on robustness which understands and control variation
4)Here there is "Frozen process," changes design space which allows continuous improvement	4) Here there is Flexible process within which always discourages



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The sequence generally recommended for method development according to QbD is

1. understanding the purpose of the study,
2. perform risk assessments to screen out factors that may or may not have an influence on the analytical method (screening variables by logic and an examination of their scientific potential for influence) and
3. characterization studies to quantify and minimize their influence on precision, accuracyand linearity.

2. ATP (Analytical Target Profile)[5]

Recognition of ATP comprises of the selection of method requirements which include target analytes (product and impurities),type of analytical technique , and specifications of the product. Preliminary risk assessment would be carried out for expectation of the method requirements and analytical criticalities.

ATP for analytical procedures comprises of

(a)selection of target analytes (API and impurities),

(b) assortment of analytical technique (HPTLC, GC, HPLC, Ion Chromatography, chiral HPLC,etc.),

(c) choice of method requirements.

***Method analytical target profile*[6]**

Method attribute	Acceptance criteria
Specificity	No interference with the main peak
Linearity	≥ 0.999 (for the known four impurities)
Relative response	Not less than 0.7
Limit of quantitation	Less than an amount corresponding to a relative peak area of 0.05%
Accuracy	Mean recovery at each level 90-110%
Precision	Absolute difference between oprators ≤ 3.0% (n=6 operator)

a)Target Analytes Selection

Many regulatory bodies and ICH Q3 enlighten the deliberation of impurities in the API synthetic route.

b)Technique Selection

Analytical technologies are wide and diverse, and although much overlap in applicability exists, each technique has strengths and weaknesses. Based upon the analytes nature suitable analytical technique can be selected. Need for the test are also important for selecting the technique.

Analytical test items and analytical techniques includes the following

1. Identification by IR: FT-IR spectrophotometer,
2. Impurity profile (Chromophore): HPLC with UVdetector,
3. Impurity profile (non-Chromophore): HPLC with RID/ELSD
4. Assay by HPLC (Chromophore): HPLC with UVdetector,
5. Assay by HPLC (non-Chromophore): HPLC with RID/ELSD

(c)Analytical method performance characteristics[7]

Method requirements can differ from one method to another. There are various method performance characteristics . There are two types of method performance, that is, systematic (bias) and inherent random (variance) components. Commmonly method performance is not evaluated by one but depends on both.

According to USP and ICH guidelines there are many validation parameters for chromatographic separations, which are considered as method performance characteristics which include accuracy and precision. These are quite commonly considered as method performance characteristics to quantify the substance. No method can be accurate and precise without adequate specificity, linearity, and peak resolutionbut these do not signify robust behavior of the method. Another vital component that one has to be establish based on acceptable behavior of both systematic and random performance characteristics is therange.

Robustness defines an operational range of method factors to give defined results. Other method performance characteristics such as linearity and specificity are not needed to be incorporated in the ATP, as they are not directly linked to understand the agreement of a measurement with the true value.

3. CQA (Critical Quality Attributes) and Initial Risk Assessment

ICH Q8(8) defines CQA as a physical, chemical, biological, or microbiological property or characteristic that should

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be within an appropriate limit, range, or distribution to ensure the desired product quality.

CQA for analytical methods comprises of method attributes and method parameters. CQA can diverge from one analytical technique to another.

a) HPLC(UV or RID) CQA are buffers used in mobile phase, pH of mobile phase, diluent, column selection, organic modifier, and elution method.

b) CQA for GC methods are oven temperature and program, injection temperature, flow of gas, sample diluent, and concentration.

c) TLC plate, mobile phase, injection concentration and volume, time taken for plate development, reagent for color development, and detection methods are the CQA for HPTLC.

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. The method performance (e.g., specificity, accuracy, precision, linearity,range, and quantitation limits for impurities) should be targeted such that the method is suitable for demonstrating measurable control of the critical quality attribute in the manufacturing process and stability testing.

4. RISK MANAGEMENT[9]:

Quality Risk Management (ICH Q9) is "a systematic process for the assessment, control, communication and review of risks to the quality

… across the … lifecycle" . Risk assessments are an vital part of the Analytical QbD process. Risk assessments smooth the progress of recognition and ranking of parameters that could brunt method performance and conformance to the ATP. Risk assessments are often iterative throughout the lifecycle of a method, and are typically performed at the end of method development, with product changes (e.g., route, formulation or process) and as a precursor to method transfer. These RAs emphasizes on potential differences (e.g., laboratory practices, environment, testing cycle times, reagents sources). During the technique selection and method development stages major differences (e.g., availability of equipment) should be recognized and factored.

4.1Methods 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 Analysis (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.

5. Method development by QbD approach

Step 1: Defining method intent

Since pharmaceutical QbD is a systematic, scientific, holistic, menace based and practical approach that begins with predefined objectives and lay emphasis on product and process understanding and control so the goals of HPLC method development have to be clearly defined.The eventual goal of the analytical method is to separate and quantify the main compound.

Step 2: Performing experimental design

Experimental design can be efficiently used for rapid and systematic method optimization.A systematic experimental design is considered necessary to aid in obtaining profound method understanding and performing optimization.. It forms a chromatographic database that will help out with method understanding, optimization, and selection. In addition, it can be used to evaluate and implement change of the method, should it be needed in the future, for example should the chromatographic column used no longer be commercially available, or an impurity is no longer relevant.

Step 3: Evaluation of experimental results and selection of final method conditions

The conditions for the method need to be evaluated using the three tiered approach. At first the conditions should be evaluated for peaks symmetry, peaks fronting and peaks tailing. Later these conditions should be further evaluated by using more stringent criteria,such as tailing factor should be less than 1.5, etc.

Step 4: Performing risk assessment with robustness and ruggedness evaluation

Once the final method is selected against method attributes, it is highly likely that the selected method is reliable and will remain operational over the lifetime of product. The fourth step of method development is mainly for the method verification and finalization and the evaluation of method robustness and ruggedness to be carried out .

A risk based approach based on the QbD principles set out in ICH Q8 and Q9 can be applied

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to the evaluation of method robustness and ruggedness. Fishbone diagram such as structured methodologies for risk assessment can be implemented to identify the potential risk of the method due to a small change of method parameters or under a variety of conditions such as different laboratories, analysts, instruments, reagents, days, etc.

6. Regulatory aspects to QbD[10]

6.1. FDA perspective

FDA's view of QbD is "QbD is a systematic approach to product and process design and development". This concept was accepted by FDA in 2004 and detailed description was given in 'pharmaceutical cGMPs for 21st century – a risk based approach'. International conference on harmonization in its Q8 pharmaceutical development, Q9 quality risk assessment and Q10 pharmaceutical quality system gives stringent requirements regarding quality of product.

FDA also states the importance of quality of pharmaceutical products by giving Process Analytical Technology (PAT) which is a Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance .QbD ultimately helps to implement Q8 and Q9. Risk-based regulatory approaches are for scientific understanding and control related process for product quality and performance.

6.2. ICH guideline and QbD

The underlying principles of QbD i.e. science- and risk-based product development, risk assessment, lifecycle approach and method design are explained in the quality guidelines of international conference on harmonization i.e. ICH Q8 *Pharmaceutical Development*, ICHQ9 *Quality Risk Management*, and ICH Q10 *Pharmaceutical Quality System.*

7. DESIGN OF EXPERIMENTS

Experimental design[11,12] can be efficiently used for rapid and systematic method optimization. Design of experiments (DOE) is a well proven vivid approach within process and product development and a key input of Quality by Design. Method development helps to understand what are the critical process parameters in the analytical method influencing accuracy and precision and to minimize their effects.

Typically DoE (Design of Experiment)[13,14] is used to find ranges for instrument operating parameters, to understand sample preparation variations and variations of method precision The ATP compiles a set of characteristics defining what analyte or analytes will be measured, in which matrix, over what concentration range(s) as well as the required performance criteria of the method together with specifications for these last ones[15-18].

DOE for method validation seek to validate the analytical method for a range of concentrations so that any changes in formulation or concentration will not require additional validation as they are changes within a characterized design space. Recently more attention has been placed on applying DOE to analytical methods.

DOE for analytical methods has three major applications:

1. Method development for new methods or those that need improvement,
2. Method validation and
3. Quantitation of the influence of analytical methods on product and process acceptance and out-of-specification rates.

QbD can be applied for various analytical methods which include,

- Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals).
- Hyphenated technique like LC–MS
- Advanced techniques like mass spectroscopy, UHPLC, and capillary electrophoresis
- Karl Fischer titration for determination of moisture content.
- Vibrational spectroscopy for identification and quantification of compounds e.g. UV method.
- Analysis of genotoxic impurity.
- Dissolution studies
- Biopharmaceutical processes

Benefits of Application of QbD Approach to Analytical Methods

Development of a robust method
✓ Applicable throughout the life cycle of the product
Regulatory flexibility
Movements within "Design Space" are not considered a change in method

8. CONCLUSION

The application of QbD concept to analytical method is justifiable, because many variables significantly affect the method results which include instrument settings, sample characteristics, method parameters, and choice of calibration

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models. Being chromatographic technique is the most common analytical tool in pharmaceutical quality control, and the number of variables involved in analytical method development phase is almost equivalent to the number of variables involved in formulation and development protocols for dosage form so implementation of QbD provides an opportunity to achieve regulatory flexibility but requires high degree of robustness, product quality, and analytical method understanding**.** Method transfer in QbD is feasible for analytical methods and will enable better, more efficient, and continuous improvements for future methods.

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