A Review on Quality by Design Approach for Analytical Method Development.

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ABSTRACT

Quality by Design is the modern approach for quality of pharmaceuticals.Recent pharmaceutical regulatory documents have stressed the critical importance of applying quality by design principles for in depth process understanding to ensure that product quality is built in by design.Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives for a product, process understanding, and process control based on knowledge and quality risk management. The purpose of this paper is to discuss the pharmaceutical quality by design and the main objective of the present review article is to describe different steps involved in method development by the QbD approach for analytical method development.In a QbD approach,the impact and interactions between critical method variables are understood using a Design of Experiments approach, multivariate analysis and modeling leading to the consistent quality by drug products.The QbD approach for method development comprises various steps that include defining method intent ,performing experimental design, evaluating experimental results,selecting proper method conditions,and performing risk assessment with changing analytical parameters and conditions for evaluation.

KEYWORDS: Quality by Design (QbD), Design ofExperiments (DOE), Risk assessment, Analytical QbD.

INTRODUCTION

QbD emphasizes the importance of building quality into the product from the beginning stages of development, rather than relying on end-product testing to ensure quality[1]. The FDA's cGMP for the 21st Century initiative promotes the use of modern quality systems and risk-based approaches to manufacturing. Process Analytical Technology (PAT) involves the use of real-time monitoring and control during production to ensure product quality[2].ICH Q8 is a guideline on pharmaceutical development that emphasizes the need for a systematic approach to product development. ICH Q9 focuses on quality risk management, while ICH Q10 emphasizes the importance of an effective quality management system. The FDA's guidance on Process Validation emphasizes the importance of establishing scientific evidence that a process is capable of consistently producing a quality product[3]. Quality by Design, manufacturers can achieve improved product quality, increased process understanding, reduced variability, and enhanced assurance of product safety and efficacy. This approach is increasingly being adopted in the pharmaceutical industry and is recognized as a key tool for ensuring the quality of products in a systematic and efficient manner.Quality by Design is a systematic approach to product development that focuses on understanding the requirements of the product and designing processes to meet those requirements, rather than simply relying on testing and inspection to ensure quality[4].Process Analytical Technology (PAT) involves the use of real-time monitoring and control during production to ensure product quality.ICH Q8 is a guideline on pharmaceutical development that emphasizes the need for a systematic approach to product development. ICH Q9 focuses on quality risk management, while ICH Q10 emphasizes the importance of an effective quality management system[5].

The key principles of Quality by Design include:

Designing and developing processes that will consistently meet product specifications.Identifying and understanding the critical quality attributes (CQAs) of the product.Designing experiments to study and optimize the critical process parameters (CPPs) that influence the CQAs[6].Using statistical tools and techniques to analyze and interpret the

experimental data.Implementing a control strategy to ensure that the process remains within the design space and produces a product of consistent quality.By following the principles of Quality by Design, manufacturers can achieve improved product quality, increased process understanding, reduced variability, and enhanced assurance of product safety and efficacy. This approach is increasingly being adopted in the pharmaceutical industry and is recognized as a key tool for ensuring the quality of products in a systematic and efficient manner., which provide recommendations for the pharmaceutical industry on how to ensure the quality of drug products The key principle of QbD is to design quality into the product from the beginning rather than relying on end-product testing to ensure quality.QbD involves a holistic and systematic approach to pharmaceutical development, starting with the identification of critical quality attributes (CQAs) that are essential for the safety, efficacy, and quality of the drug product. These CQAs are then used to define the target product profile (TPP) and the quality target product profile (QTPP), which outline the desired characteristics of the final product.Throughout the development process, QbD emphasizes the importance of understanding the relationship between critical process parameters (CPPs) and CQAs, as well as the impact of raw materials, manufacturing processes, and other factors on product quality. By utilizing QbD concepts, such as understanding the critical quality attributes (CQAs) of a product, identifying critical process parameters (CPPs), and developing a control strategy based on scientific understanding, manufacturers can ensure that their product meets the desired quality attributes consistently. Additionally, the use of quality and statistical tools and methods within the QbD framework can help to optimize method performance, improve method robustness, and facilitate method validation. By using statistical designs of experiments, multivariate statistics, and statistical quality control techniques, analytical scientists can efficiently explore the effects of critical method parameters, evaluate interactions between parameters, and monitor method performance over time. This allows for a more efficient and effective development process, as potential issues can be identified and addressed early on in the design. The phase transition from QbT to QbD represents a strategic shift towards a more proactive and efficient approach to quality management, with the ultimate goal of achieving higher quality products, improved processes, and greater regulatory flexibility The context of HPLC method development, QbD involves identifying critical method parameters (e.g. mobile phase composition, column temperature, flow rate, etc.) and establishing their acceptable ranges through systematic experimentation. By using statistical tools and design of experiments (DoE) approaches, scientists can optimize the method to ensure that it meets predefined criteria for performance and reliability.Furthermore, QbD practices also include the establishment of a thorough understanding of the method's performance characteristics, such as selectivity, sensitivity, linearity, accuracy, and precision. By systematically evaluating these parameters and establishing appropriate acceptance criteria, scientists can ensure that their HPLC methods are fit for purpose and capable of consistently delivering accurate and reliable results.Establishing robustness and ruggedness during method development is important for ensuring the reliability and reproducibility of the analytical method. This can help prevent costly and time-consuming issues such as method failure, out-of-specification results, and the need for method revalidation However, with the implementation of QbD principles, the use of DoE methodology has become more widespread in method development. By using DoE, multiple factors can be evaluated simultaneously and interactions between factors can be identified, leading to a more efficient and optimized method development process.Additionally, chemometrical tools such as multivariate data analysis can be used to analyze complex data sets and extract meaningful information. These tools can help identify critical process parameters and potential risks, leading to a more robust control strategy.the use of experimental design plans and software modeling packages in HPLC method development can lead to more robust and efficient methods with improved selectivity and resolution. This approach also allows for better understanding of the underlying interactions between factors, leading to more reliable and transferable methods across different labs. By incorporating advanced statistical and computational tools, chromatographers can streamline the method development process and achieve better results in a more systematic and efficient manner..

2. ATP(Analytical Target Profile)

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.

a)Target AnalytesSelection

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 forselecting 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,assay by HPLC (non-Chromophore): HPLC with RID/ELSD

(c)Analytical method performance characteristics

Method requirements can differ from one method to another. There are various method performancecharacteristics . There are two types of methodperformance, that is, systematic (bias) and inherentrandom (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. Anothervital 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 and initial risk assessment

a physical, chemical, biological, or microbiological property or characteristic that shouldbe within an appropriate limit, range, or distribution toensure the desired product quality.CQA for analytical methods comprises of method attributes and method parameters. CQA can divergefrom 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 andprogram, injection temperature, flow of gas, samplediluent, and concentration.

c) TLC plate, mobile phase, injection concentration andvolume, time taken for plate development, reagentfor color development, and detection methods are theCQA for HPTLC.Physical and chemical properties of the drug substanceand impurities such as polarity, charged functional groups, solubility, pH value, boiling point, andsolution 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.RISKMANAGEMENT[10].

Quality Risk Management (ICH Q9) is “a systematprocess for the assessment, control, communicationand reviewofrisks to the quality… across the … lifecycle” . Risk assessments are anvital 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 lifecycleof 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,reagentssources). 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 ICHguideline 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[7].

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 emphasison product and process understanding and control so the goals of HPLC method development haveto 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 forrapid and systematic method optimization.Asystematic experimental design is considered necessary to aid in obtaining profound method understanding and performing optimization.. It forms a chromatographic database that will help outwith method understanding, optimization, anselection. 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 becommercially available, or an impurity is no longerelevant.
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 firstthe 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 withrobustness 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 QbDprinciples set out in ICH Q8 and Q9 can be applied to the evaluation of method robustness and ruggedness. Fishbone diagram such as structuredmethodologies for risk assessment can beimplemented to identify the potential risk of the method due to a small change of method parameters orunder a variety of conditions such as different laboratories, analysts, instruments, reagents, days, etc.

6. Regulatory aspects toQbD
6.1.FDA perspective[8].
"s view of QbD is "QbD is a systematicapproach to product and process design and development". This concept was accepted by FDA in2004 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 qualityof product.FDA also states the importance of quality ofpharmaceutical products by giving Process AnalyticalTechnology (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 andperformance.
6.2. ICH guideline andQbD
The underlying principles of QbD i.e. science- andrisk-based product development, risk assessment,lifecycle approach and method design are explained inthe 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[9].

Experimental design 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 akey input of Quality by Design. Method developmenthelps to understand what are the critical processparameters 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 DOE for method validation seek to validate theLanalytical method for a range of concentrations so that any changes in formulation or concentration will not require additional validation as they are changeswithin a characterized design space. Recently moreattention has been placed on applying DOE t ofo analytical methodsDOE for analytical methods has three major applications(15-16).

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,

1 Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals).

2 Hyphenated technique like LC–MS

3 Advanced techniques like mass spectroscopy, UHPLC, and capillary electrophoresis, Karl Fischer titration for determination of moisture content.

4 Vibrational spectroscopy for identification and quantification of compounds e.g. UV method. Analysis of genotoxic impurity.

5 Dissolution studies

6 Biopharmaceutical processes.

Table : Pharmaceutical aspects : traditional vs .QbD

Aspect	Traditional	QBD
Pharmaceutical development	Empirical	Systematic ; Multivariate experiment
Manufacturing process	Fixed	Adjustable within design space ;opportunities for innovation
Process control	In process testing for go /on go ; offline analysis wide or slow response	PAT utilized for feedback and feed forward at real time
Product specification	Primary means of quality control ;based on batch data	Part of the overall control strategy ;based on the desired product performance
Control strategy	Mainly by intermediate product and end product testing	Risk based ; controlled shift up stream ,real time release
Lifecycle management	Reactive time problem and OOS ;post approval changes needed.	Continual improvement enabled within design space.

Benefits of implementing QbD for FDA[11].

1. Enhance scientific foundation for review .
2. Provides for better coordination across review, compliance and inspection.
3. Improves information in regulatory submissions .
4. Provides for better consistency .Improves quality of review (establishing a QMS for CMC) .
5. Provides for more flexibility in decision making .
6. Ensures decisions made on science and not on empirical information .
7. Involves various disciplines in decision making .
8. Uses resources to address higher risks .

BENEFITS TO INDUSTRY[12].

1. Ensures better design of products with less problems in manufacturing .
2. . Reduces number of manufacturing supplements required for post market changes –rely on process and risk understanding and risk mitigation .
3. Allows for implementation of new technology to improve manufacturing without regulatory scrutiny .
4. Allows for possible reduction in overall costs of manufacturing –less waste .
5. Ensures less hassle during review –reduced deficiencies –quicker approvals .
6. Improves interaction with FDA –deal on a science level instead of on a process level .

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 calibrationmodels. 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 regulatoryflexibility 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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