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A REVIEW ON QUALITY BY DESIGN APPROACHES TO ANALYTICAL METHOD DEVELOPMENT

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ABSTRACT

Quality by Design (QbD) refers to a holistic approach towards the drug development. In pharmaceutical industries drug development is important and critical to achieve the best quality. New drug development we should follow Quality by Design approach. Most of regulatory agency and or FDA are reviewing the drug development data. To answer such agencies and FDA we have to go towards a more scientific, risk based, holistic and proactive approach. Industrial concepts are to understand the product and manufacturing process, starting with product development, basically building quality in, not testing it. Under this concept of QbD during designing and development of a product, Now-a-days the concept of QbD can be extended to analytical techniques. Under this concept of QbD throughout designing and development of a product, it is essential to define desire product performance profile, Target product Profile (TPP), Target Product Quality Profile (TPQP)] and identify critical quality attributed (CQA). This paper gives idea about the Pharmaceutical QbD and describes use of Quality by Design to ensure quality of Pharmaceuticals. Recently the concept has been also appreciated by different regulatory, especially by EMA (Europe Medicines Agency) and other ICH countries authorities over the globe. They are very popularly accepted as AQbD (Analytical Quality by Design) concepts by the industry.

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INTRODUCTION

The pharmaceutical manufacturing is one of the main strictly regulated and governed sector by authoritative regulatory bodies, because quality of pharmaceuticals directly related to the health of the public. 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. Quality is nothing but ability to fulfill the needs and expectations of the customer. Customer demands the excellence in quality, consistency, low cost and timely performance. The word quality is originated from Latin word 'qualis' means 'of what kind'. 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 information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls. Information from pharmaceutical development studies can be a basis for quality risk management. In all cases, the product should be designed to meet patient's needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development, or a combination of both. The Food and Drug Administration (FDA) and pharmaceutical industry are talking about quality by design, and there are many important terms that are used as part of this discussion. However, industry comments indicate that there is still much confusion in the generic industry as to the meaning of quality by design and its associated nomenclature. Before implementation of QbD in the pharmaceutical industry the practice was to carry out off-off-line analysis for in-process testing as per the product specific need and product specifications were considered as the primary means of control. This was resulted in unpredictable scale up issues. Also the cost of revalidation and supplementary approvals was used to be more. But now due to implementation of QbD the scenario is changing. The Pharmaceutical industry has now started using systematic approach to development that begins with predefined objectives and emphasizes on products and process understanding for process control. In this paper, we provide a consistent set of definitions to provide a clearer understanding of quality by design for abbreviated new drug applications (ANDAs).

Analytical method development and validation plays a very crucial role in product development. A robust analytical method not only assures whether the quality of drug is achieved as per the intended therapeutic use but also serves as a purity check at each stage of product development life cycle. With the commercial manufacturing of product it is important that the analytical method is time saving as well as robust and accurate since the release in market is decided on final quality control results of finished product accompanied by other data of the batch. Analytical techniques widely include estimation of physical, chemical, physicochemical, and/or 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 very widely known as they have various advantages over other non-chromatographic methods. They are versatile, robust, and require fewer amounts of samples. With the use of automation these techniques minimize the probability of human error.

The main concern of the analytical chemist is to develop a suitable analytical method that exactly works as per the intended use. In the current scenario of analytical chemistry, there are two approaches followed for analytical method development. The former is based on trial and error which studies one factor at a time (OFAT), where one parameter alone is optimized for the expected response whilst others remained constant. This practice always yields a narrow robust behavior of the method for instrumental variables used in method development phase. Hence the strategy of analytical method (i.e. OFAT) development has high risk in method failure and always requires revalidation protocol after method transfer or during alternative method development; thereby it has been increasing the cost of the method. The later approach is Analytical Quality by Design (AQbD) which explores scientific understanding in method implementation sequences and starts with product quality that relates the risk assessment in method choice and then between method parameter and expected method results and finally a region for high robust and cost effective approach. Design of Experiment (DoE) is a part of AQbD, and it represents the interaction among the input variables that ultimately affect the method response and results. AQbD paradigm is a preferred and recommended strategy to be followed in analytical method development so as to attain regulatory flexibility and reduce Out of specification (OOS), Out of term (OOT) and Out of control (OOC) results and when this approach is used to study any chromatographic method, the methods explores more knowledge of the parameters that has to be controlled and monitored during the life cycle of the method.

Advantages of QbD can be summarized as,

- Patient safety and product efficacy are focused.
- Scientific understanding of pharmaceutical process and methods is done.
- It involves product design and process development.
- Science based risk assessment is carried.
- Critical quality attributes are identified and their effect on final quality of product is analyzed.
- It offers robust method or process.
- Business benefits are also driving force to adopt QbD.

List of regulatory Guidelines/Activities:

Historically, designing or building the quality into products had been a necessity for complex manufacturing operations, like, aircraft manufacturing. However, in pharmaceutical development, it formally started with release of a guidance document entitled 'Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach', by USFDA in August, 2002. Since then, a lot has happened in pharmaceutical QbD area resulting in issue of multiple regulatory guidelines, which are listed in Table. It also includes other QbD-related activities being carried out by various other agencies indulged in improving/regulating the quality of pharmaceuticals.

Table No.: 01 List of regulatory Guidelines/Activities.

Agency	Guidelines/Activities	Month Year
USFDA	Pharmaceutical cGMP for the 21st Century - A Risk-Based Approach: Second Progress Report and Implementation Plan	Sep 2003
USFDA	Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance	Sep 2004
USFDA	Pharmaceutical cGMP for the 21st Century - A Risk-Based Approach: Final Report	Sep 2004
EMA	The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future	March 2005
ICH	Pharmaceutical Development (Q8)	Nov 2005
ICH	Quality Risk Management (Q9)	Nov 2005
ICH	Pharmaceutical Quality System (Q10)	June 2008
ICH	Pharmaceutical Development (Q8(R2))	Aug 2009
WHO	Quality Risk Management	Aug 2010
EMA	Guidance for Industry: Process Validation: General Principles and Practices	Jan 2011
EMA-USFDA	EMA-FDA pilot program for parallel assessment of Quality by Design applications	March 2011
ICH	ICH-Endorsed Guide for ICH Q8/Q9/ Q10 Implementation	Dec 2011
EMA	ICH Quality IWG Points to consider for ICH Q8/Q9/Q10 guidelines	Feb 2012
EMA	Guideline on Real Time Release Testing (formerly Guideline on Parametric Release)	March 2012
EMA	Guideline on Process Validation (draft)	March 2012
USFDA	Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms	April 2012
ICH	Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological entities) (Q11)	May 2012
EMA-USFDA	EMA-FDA pilot program for parallel assessment of Quality-by-Design applications: lessons learnt and Q&A resulting from the first parallel assessment	Aug 2013
EMA	Guideline on process validation for finished products - information and data to be provided in regulatory submissions	Feb 2014

Building blocks of QbD:

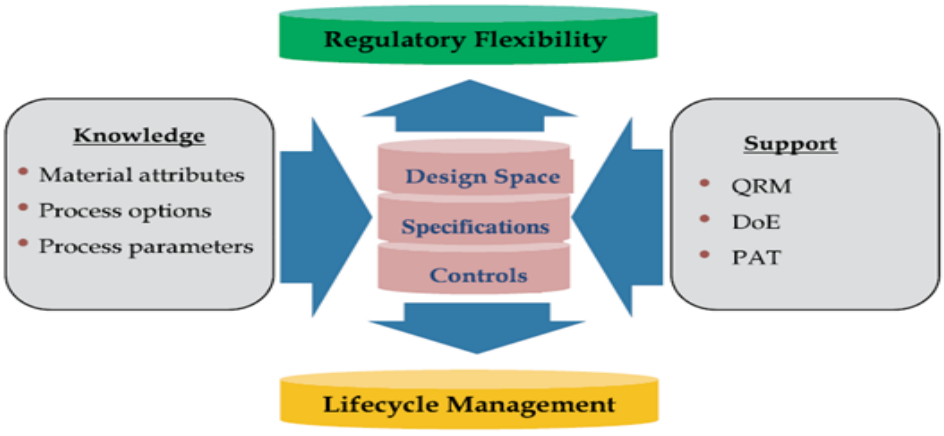

Figure 1: Building blocks of Quality by Design (QbD).

Key terms: QRM: Quality Risk Management; DoE: Design of Experiments; PAT: Process Analytical Technology

Regulatory guidelines or other QbD related activities

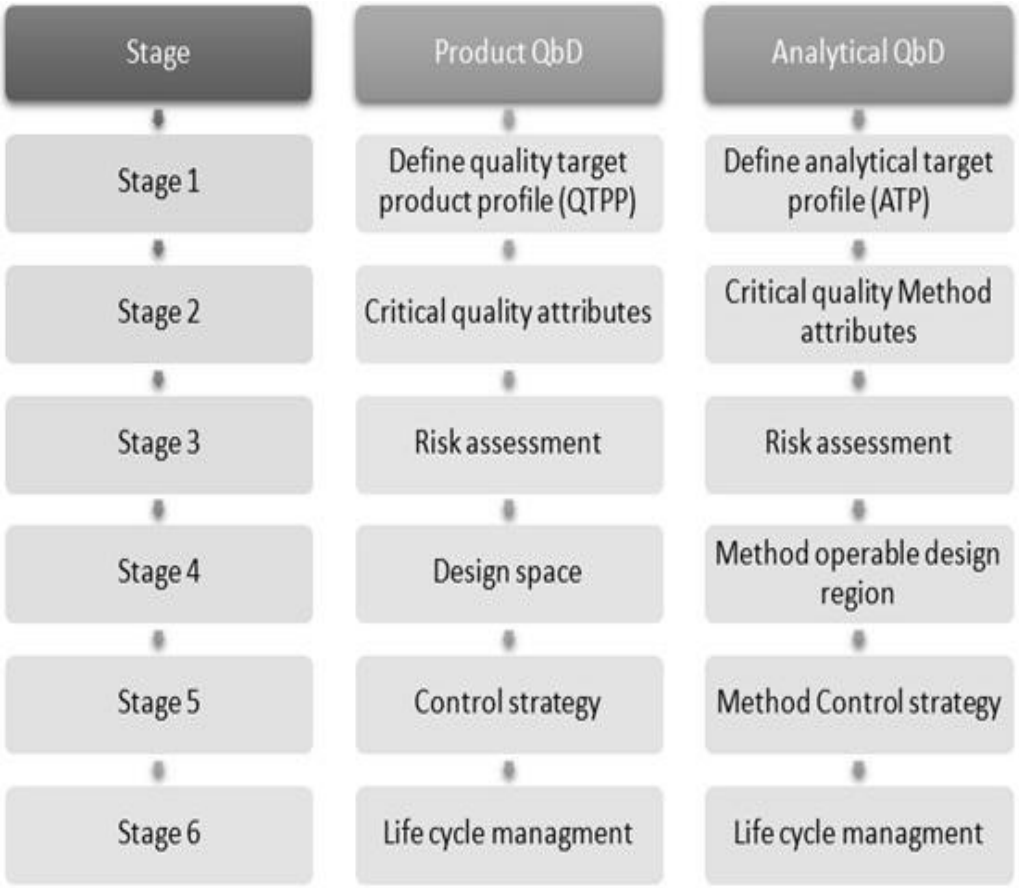

Figure 2: Regulatory perspective of QbD vs AQbD.

Steps involved in QbD:
Development of new molecular entity
- Preclinical study
- Nonclinical study
- Clinical Study
- Scale up
- Submission for market Approval

Manufacturing
- Design Space
- Process Analytical Technology
- Real time Quality Control

Control Strategy
- Risk based decision
- Continuous Improvement
- Product performance

Seven steps of QbD startup plan:

1. Hire an independent Quality by design expert.
2. Audit your organization and process with the expert conducting a gape analysis.
3. Hold a basic quality by design workshop with all your personal.
4. Review the expert's report and recommendation.
5. Draft an implementation plan, timelines and estimated costs.
6. Assign the resources (or contract out).
7. Retain the independent expert as your "Project Assurance" advisor.

Key aspects of QbD:

Target Product Quality Profile (TPQP):

The Target Product Quality Profile (TPQP) is a tool for setting the strategic foundation for drug development "planning with the end in mind." More recently an expanded use of the TPP in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management has started to evolve.

Target Product Profile (TPP):

TPP is an abstract of the essential properties of the drug and its intended use. These properties define the objectives of the drug development programed. TPP serves as a planning instrument to assist the lead development team to design strategies for medicinal chemistry, pharmacology, toxicology, formulation, etc. It plays a principal role in the total drug discovery and development process by successful optimization of a drug candidate, decision-making within an organization, design of clinical research schedules, and constructive correspondence with the regulatory. TPP eventually summarizes the drug's pharmacology, indications, usage, routes of administration and adverse effects of the dose. It links the drug development activities with the labelled specifications.

Quality Target Product Profile (QTPP):

It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised on the label. It includes identity, assay, dosage form, purity and stability. The QTPP guides the formulation scientists to establish formulation strategies to develop a product of optimum quality. QTTP forms the basis for design and development of the product.

QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. More recently an expanded use of the TPP in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management has started to evolve. The TPP can play a central role in the entire drug discovery and development process such as:

1. Effective optimization of a drug candidate
2. Decision-making within an organization
3. Design of clinical research strategies, and
4. Constructive communication with regulatory authorities.
5. The TPQP guides formulation scientists to establish formulation strategies and it will keep the formulation effort to be focused and efficient.

Elements of Analytical QbD:

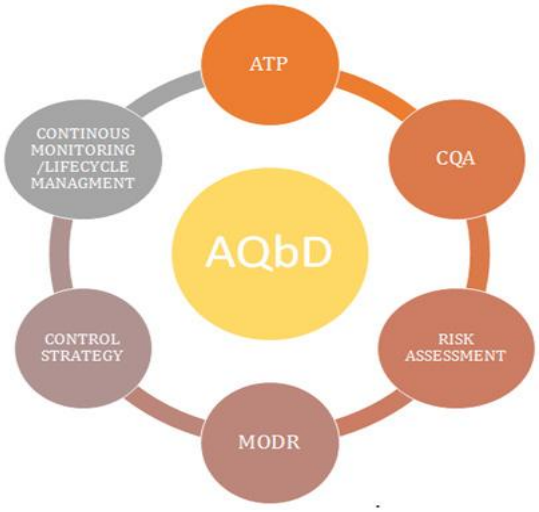

Figure 3: Elements of Analytical QbD.

AQbD/QbD comprises of all elements of pharmaceutical development described in ICH Q8 depicted in above Figure.

Analytical target profile:

ATP is way for method development or it is simply a tool for method development and has been mentioned in the ICH Q8R guidelines. In general the goal of the chromatographic method is separation, quantification and identification of drug substance, impurity or degradant. Impurity is considered to be the critical quality attribute (CQA). While dealing with traces of impurities it will be beneficial to have knowledge of previous synthetic and manufacturing processes and all other possible pathways which lead to the encounter of impurities. The method requirements will be the accuracy precision, robustness, ruggedness and so on as described in ICH guideline. Whether it is a conventional method or QbD method detailed information of compound should be collected like its solubility, pKa, pH, UV chromophore, and stability.

Method Design:

Method design is prepared for appropriate availability of material and setting various experimental conditions. In this the reagents required are made available. Regional and geographical conditions are taken into consideration. Feasibility of instruments is checked and experimental design is prepared. In case of HPLC method development scouting is done. In this large number of experimental conditions were tried (pH, temperature, columns, and buffers).

Data are collected and software is generated by entering obtained results in terms of values from actual experiments. Then that data base is generated which helps to predict the effect of various chromatographic conditions in large number. This type of software helps to predict outcome without actual experimentation. Response from design also includes resolution and run time. Hence it is cost effective as well as time effective. Software also assists the future changes in method. Method design also involve selection of different analytical techniques that can be used for particular method development; for example different instrumental method that can be opt like HPLC, LC, Raman and the most effective method amongst is chosen. Among various methods; suitable method to serve the desired purpose is chosen.

Method development strategy (MDS) includes design of experiments (DoE). It is helpful in risk assessment by gaining knowledge about existing method and allows for effective control strategies for critical parameter. Method design is made considering the ICH guidelines for validation hence validation remains formality. Simultaneously evaluate several factors at given numbers of levels in a predefined number of experiments. Experimental designs are as follows,

- Full factorial,
- Fractional factorial,
- Plackett–Burman designs

CQA (Critical Quality Attributes):

ICH Q8 defines CQA as a physical, chemical, biological, or microbiological property or characteristic that should 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 differ from one analytical technique to another.

- CQA for HPLC (UV or RID) are buffers used in mobile phase, pH of mobile phase, diluent, column selection, organic modifier and elution method.
- CQA for GC method is oven temperature and its program, injection temperature, flow rate of gas, sample diluent and concentration.
- CQA for HPTLC is TLC plate, mobile phase, injection concentration and volume, time taken for plate development, reagent for color development, and detection methods.

Physical and chemical properties of the drug substance and impurities can also describe CQA for analytical method development such as polarity, charged functional groups, solubility, pH value, boiling point and solution stability.

Factors which directly affect the quality & safety of the product are first sorted out, and its possible effect on method development is studied. Understanding of the product and method will help to sort the CQA. If drug product contains the impurity which may have direct effect on quality and safety of drug product it is being considered the critical quality attribute for the HPLC method development of that particular drug compound. Safety and specification, intermediate specification, and process control efficacy can be achieved by demonstrating measurable control of quality attributes i.e. product.

Risk Assessment:

Risk assessment strategy as 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 is vital in order to reach a confidence level that the method is reliable. Once the technique is identified, AQbD emphases on detailed risk assessment of the factors that may lead to possible variability in the method, like analyst methods, instrument configuration, measurement and method parameters, sample characteristics, sample preparation, and environmental conditions.

It is link between input process variable and CQA. Various tools for risk assessment are,

1. Ishikawa or fishbone diagram,
2. Failure mode effect analysis (FMEA),
3. Pareto analysis.

An Ishikawa or fishbone diagram is used to identify all potential variables, such as raw materials, instrumental factors, and environmental factors, which can have an impact on a particular CQA. A FMEA can then be used to rank the variables based on risk (i.e. a combination of probability, severity, and delectability) and to select the process parameters with higher risks for further studies to gain greater understanding of their effects on CQAs.

Main aim of chromatographic method development is separation and identification of compound. In QbD approach the emphasis is given on rugged and robust method through risk assessment. Small changes in method parameter like reagents, instruments, analyst, laboratories, days, temperature, and humidity are included in risk assessment. Available tools for analysis of data are Design of Experiments (DoE) and Method System Analysis (MSA). If the primary method fails, then a backup method is risk-assessed until a suitable method is identified. If both methods are challenging each other in advantages then methods are weighed against robustness and ruggedness for choosing best method.

Principles of quality risk management are:

- Scientific knowledge based evaluation of the risk to quality which eventually links to the protection of the patient.
- Adequate effort should be taken; formality and documentation of the quality risk management process should be done with the level of risk involved.

Traditional method development relied on testing the method after transfer whereas Analytical QbD demands the risk assessment step before method transfer and throughout the product life cycle. According to ICH Q9, risk assessment can be carried out in three steps viz., risk identification, risk analysis and risk evaluation. Accordingly the risk factors are classified into the following categories:

- High Risk Factors: e.g. Sample preparation methodology. These are to be fixed during the Method Development process.
- Noise Factors: These are subjected to an MSA study. It can be done through staggered cross nested study design and variability plots, ANOVA etc. These factors are subjected to robustness testing.
- Experimental Factors: e.g. Instrumentation and operation methods. Subjected to ruggedness testing and acceptable range is identified. The third step is Risk Evaluation which is done through Failure mode and effects analysis (FMEA) and the Matrix designs.

For impurity profiling by HPLC method staggered cross nested design was used and for Karl Fisher Titration (KFT) Method System Analysis (MSA) was found to be useful. Design of experiment was done for the robustness studies.

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 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.

Method qualification

Once the method is designed keeping analytical target profile (ATP) in mind with taking care of the risk involved in development, the next step comes is method qualification this is to ensure that method is being performed as intended. It involves equipment qualification which is part of method qualification. It is divided in, method installation qualification (MIQ), method operational qualification (MPQ), and method performance qualification (MPQ).

For demonstration of instrumental qualification HPLC instrument is considered. While developing a chromatographic method on HPLC following qualification can be done.

Installation Qualification (IQ)

Installation Qualification is a documented collection of activities needed to install an instrument in the user's environment. IQ applies to a new, pre-owned or an existing on-site—but not previously qualified instrument. The activities and documentation associated with IQ are as follows:

System Description

Provide a description of the instrument, including its manufacturer, model, serial number, software version, etc. Use drawings and flowcharts where appropriate.

Instrument Delivery

Ensure that the instrument, software, manuals, supplies, and any other accessories arrive with the instrument as the purchase order specifies and that they are undamaged. For a pre-owned or existing instrument, manuals and documentation should be obtained.

Utilities/Facility/Environment

Verify that the installation site satisfactorily meets vendor-specified environmental requirements. A commonsense judgment for the environment suffices; one need not measure the exact voltage for a standard-voltage instrument or the exact humidity reading for an instrument that will operate at ambient conditions.

Network and Data Storage

Some analytical systems require users to provide network connections and data storage capabilities at the installation site. If this is the case, connect the instrument to the net-work and check its functionality.

Assembly and Installation

Assemble and install the instrument and perform any initial diagnostics and testing. Assembly and installation of a complex instrument are best done by the vendor or specialized engineers, whereas users can assemble and in-stall simple ones.

Installation Verification

Perform the initial diagnostics and testing of the instrument after installation. On obtaining acceptable results, the user and (when present) the installing engineer should con-firm that the installation was successful before proceeding with the next qualification phase.

Operational Qualification (OQ)

After a successful IQ the instrument is ready for OQ testing. The OQ phase may consist of these test parameters:

Fixed Parameters

These tests measure the instrument's no changing, fixed parameters such as length, height, weight, etc. If the vendor-supplied specifications for these parameters satisfy the user, he or she may waive the test requirement. However, if the user wants to confirm the parameters, testing can be performed at the user's site. Fixed parameters do not change over the life of the instrument and therefore never need predetermining.

Secure Data Storage, Backup, and Archive

When required, secure data handling, such as storage, backup, and archiving should be tested at the user site according to written procedures.

Instrument Functions Tests

Test important instrument functions to verify that the instrument operates as intended by the manufacturer and required by the user. The user should select important instrument parameters for testing according to the instrument's intended use. Vendor-supplied information is useful in identifying specifications for these parameters. Tests should be designed to evaluate the identified parameters. Users, or their qualified designees, should perform these tests to verify that the instrument meets vendor and user specifications.

The extent of OQ testing that an instrument undergoes de-pends on its intended applications. We therefore offer no specific OQ tests for any instrument or application. Nevertheless, as a guide to the type of tests possible during OQ, consider these, which apply to a high-performance liquid chromatography (HPLC) unit:

- Pump flow rate
- Gradient linearity
- Detector wavelength accuracy
- Detector linearity
- Column oven temperature
- Peak area precision
- Peak retention time precision

Performance Qualification (PQ)

After the IQ and OQ have been performed, the instrument's continued suitability for its intended use is proved through performance qualification. The PQ phase includes these parameters:

Performance Checks

Set up a test or series of tests to verify an acceptable performance of the instrument for its intended use. PQ tests are usually based on the instrument's typical on-site applications. Some tests may resemble those performed during OQ, but the specifications for their results can be set differently if required. PQ tests are performed routinely on a working instrument, not just on a new instrument at installation. Therefore, PQ specifications can be slightly less rigorous than OQ specifications. Nevertheless, user specifications for PQ tests should evince trouble-free instrument operation vis-à-vis the intended applications

Preventive Maintenance and Repairs

When PQ test(s) fail to meet specifications, the instrument re-quires maintenance or repair. For many instruments a periodic preventive maintenance may also be recommended. Relevant PQ test(s) should be repeated after the needed maintenance or repair to ensure that the instrument remains qualified.

Development of experimental design

Experimental design is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Design space is proposed by the applicant and is subject to regulatory assessment and approval of ICH Q8 (R2). Pharmaceutical development scientists have began making use of computer-aided process design (CAPD) and process simulation to support process development and optimization of manufacturing.

Operation within the design space will result in a product meeting the defined quality. Independent design spaces for one or more unit operations can be applied; a single design space can be applied for multiple operations. Different mathematical models are available for design of experiment like Placket– Burman, Box Behnken, Taguchi, Surface Design, Full and fractional factorial designs. Full factorial design was used to study the effect of formulation factors on pharmaceutical properties of tablet; in that independent variables were binder and disintegrant concentration, resistance to crushing while dependant variable was drug release. Such a multidisciplinary approach is beneficial as manufacturing process improvement can be done in previously approved space; it decreases number of variation after marketing. It is a risk based approach which is based on timely quality control rather than final testing of finished product.

Designing and implementing control strategy

Control strategy is required to ensure that material and process are within the expected lower and upper limits. Parameter and material are routinely controlled during production in order to assure reproducibility. The control space should be within the design space. Generally scale up is trial and error basis. During scale up processes parameters may differ but attributes which affect quality remain the same hence control strategy is required. QbD gives trace on reproducibility and robustness. Process capability index expresses reproducibility of process.

Process capability index (CpK) = Upper limit of specification - lower limit of specification / 6standard deviation

Establishing a control strategy is of utmost importance while ensuring that the method is performing as intended on a routine basis as goals described in ATP. Basically it's a planned set of controls aimed at minimizing the variability in the process. The strategy is data dependent. Data generated during method development and method verification forms the basis of the control strategy. A factor identified to have risk has to be controlled. More attention is given to the high risk factors. If the risk are low and manageable then the method control strategy can be defined, which generally consists of appropriate system suitability check and verified time to time by having control over it so that method delivers the desirable method attributes.

Control space should be within the design space, it is an upper and lower limit for raw material or a process within which parameter and material are regularly controlled which assures quality of product. Design space cover control space (Fig. 5). If control space is smaller than design space it is considered as robust. Usually in process quality control tests are performed to examine quality and trace out defects but QbD approach being proactive in the initial steps the potential attributes which could possibly give out of range result and affect the quality are identified. Deliberate variations in those attributes are studied in design space.

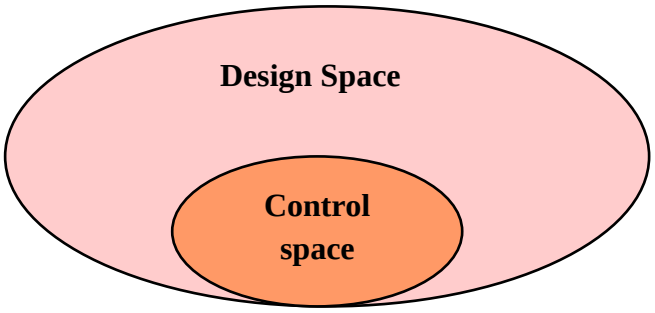

Figure 4: Control space within the design space.

Lifecycle Management

Going through all the elements of AQbD for a particular analytical method the key steps that ensure fitness of the method for its intended use includes the method validation, verification and transfer. Combining all together is termed as 'lifecycle management of analytical procedure', which commence with establishment of ATP and continues till the methods are in use. The resultant confirmation with respect to ATP is the main focus of performance qualification e.g., precision study at the site of routine use. Continual verification involves activities, which provide the assurance that the method is under control throughout its lifecycle.

Product quality can be improved throughout the product lifecycle; companies have opportunities to opt inventive approaches to improve quality. Process performance can be monitored to make sure consistency in quality. Additional experience and knowledge is gained during routine manufacture which contributes to method/process development.

Application of QbD in analytical methods of measurement

''QbD does not necessarily mean less analytical testing'' rather, it means the right analysis at the right time, and is based on science and risk assessment. Implementation of QbD helps to develop rugged and robust method which helps to comply with ICH guideline hence for that reason pharmaceutical industries are adopting this concept of QbD. This approach facilitates continuous improvement in method. Though it is not adopted by all pharmaceutical industries it has future perspective because it may become mandatory by regulatory bodies. Voluntary adoption of this concept by industries is possible because of its various benefits, and ease of compliance with regulatory authorities. Pharmaceutical research and manufactures of America (PhRMA), Analytical Technical group (ATG) and European Federation of Pharmaceutical Industries and Association (EFPIA) have given clear ideas about parallel implementation of QbD to analytical method. 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.
- To biopharmaceutical processes.

Potential benefits of adopting QbD for analytical method

1. Scientific understanding of pharmaceutical process and method.
2. It provides a space for invention of new techniques by continuous improvement throughout life cycle.
3. Critical quality attributes are identified and their effect on final quality of product is analyzed.
4. It provides required design space for development.
5. Flexibility in analysis of API, impurities in dosage forms, stability samples, and metabolites in biological samples.
6. Reduction in variability in analytical attributes for improving the method robustness.
7. Minimize deviations and costly investigations.
8. Smooth process of method transfer to the production level.
9. It provides greater compliance with regulatory authorities.

Literature reports of application QbD or elements of QbD to analytical method

Dennis Asberg envision a regulatory approved analytical QC method that can be continuously improved, even with minor changes outside the original design space, which is not yet possible. This is demonstrated by switching from HPLC to UHPLC using the same mATP for both methods. It present a method enhancement concept which allows minor adjustments, within the same measuring principle, outside the original MODR without interaction with regulatory agencies. The feasibility of the concept is illustrated by a case study of a QC-method based on HPLC, assumed to be developed before the introduction of UHPLC, where the switch from HPLC to UHPLC is necessary as a continual improvement strategy. The concept relies on the assumption that the System Suitability Test (SST) and failure modes are relevant for other conditions outside the MODR as well when the same measuring principle is used**.**

Alifiya S. Rajkotwala study describes the development of a comprehensive science and risk based HPLC method and subsequent validation for the analysis of Piracetam active pharmaceutical ingredient (API) using a quality by design approach. An efficient experimental design based on systematic scouting of two key components of the RP-HPLC method (mobile phase and pH) is presented. The stock solution Piracetam was made in methanol and absorption maximum of standard solution of Piracetam was found be 205 nm. The chromatographic condition were optimized with design expert software 10.0 version, i.e.; column C18, mobile phase used buffer (pH 6.5): Acetonitrile+0.1% TEA (80:20), flow rate was 1 ml/min. The described method was linear (R2= 0.998) with range 20-70 µg/ml. The precision, ruggedness and robustness values were also within the prescribed limits (<1% for system precision and <2% for other parameters). Chromatographic peak purity results indicated the absence of co-eluting peaks with the main peak of Piracetam. The proposed method can be used for routine analysis of Piracetam in quality control laboratories.

BV Girish he purpose of this study was to implement QbD (quality by design) principles to develop a simple, sensitive and rapid RP-UPLC (Reversed phase Ultra Performance Liquid Chromatography) method for the separation and quantification of Dimenhydrinate impurities in its dosage form, Dimenhydrinate ODT (Orally disintegrating tablets).The method was developed with predefined analytical target profile. The method employs XSelect HSS T3 (100*2.1mm, 1.8 µm) chromatographic column with Mobile phase A as mixture of Phosphate buffer pH 2.5: Acetonitrile (65:35) and Mobile phase B, a mixture of Phosphate buffer pH 2.5: Methanol (5:95) in gradient run. The injection volume was 2µl with column temperature of 30ºC and working wavelength of 225nm. The composition of mobile phases and gradient program were evaluated through DOE. Main effects of percentage Acetonitrile in Mobile phase A, percentage Methanol in Mobile phase B, gradient steepness and their interaction effects on critical quality attributes (CQA) were established. The design space for the method was established through CCD (Central Composite Design) statistical model. The QbD compliant method was successfully developed and validated for Specificity, Linearity, Accuracy, Repeatability, Range, Limit of detection and quantitation. The method was proved for its stability indicating nature by forced degradation studies.

Monika L. Jadhav develop Chromatographic and spectrophotometric methods were developed according to Quality by Design (QbD) approach as per ICH Q8 (R2) guidelines for estimation of propafenone hydrochloride in tablet dosage form. QbD approach was carried out by varying various parameters and these variable parameters were designed into Ishikawa diagram. The critical parameters were determined by using principal component analysis as well as by observation. Estimated critical parameters in HPTLC method include solvent methanol, mode of detection absorbance, precoated aluminium backed TLC plate (10 cm × 10 cm), wavelength: 250 nm, saturation time: 20 min, band length: 8 mm, solvent front: 70 mm, volume of mobile phase: 5 mL, type of chamber: 10 cm × 10 cm, scanning time: 10 min, and mobile phase methanol: ethyl acetate: triethylamine (1.5: 3.5: 0.4 v/v/v). Estimated critical parameters in zero order spectrophotometric method were solvent methanol, sample preparation tablet, wavelength: 247.4 nm, slit width: 1.0, scan speed medium, and sampling interval: 0.2, and for first order derivative spectrophotometric method it was scaling factor: 5 and delta lambda 4. The above methods were validated according to ICH Q2 (R1) guidelines. Proposed methods can be used for routine analysis of propafenone hydrochloride in tablet dosage form as they were found to be robust and specific.

Problems in adoption of QbD

1. Internal unwillingness in company
2. Lack of belief in a business case. It is assumed that QbD would require more time to file generic products or that the amount of clinical trials necessary to implement QbD for drug substance production
3. Lack of technology to implement.
4. Alignment with third parties. It is difficult to manage a multipart supply chain that includes both suppliers and contract manufacturers.
5. Inconsistent treatment of QbD across FDA. It is believed that FDA may not review filings in a consistent manner.
6. Lack of concrete guidance for industry. Companies wanted clarification from FDA on matters such as acceptable methods, criteria to select critical quality attributes, standards by which to judge adequacy of controls, and criteria for analytical method substitution.
7. Regulators not ready to handle QbD applications.
8. Presented regulatory benefits does not inspire to follow QbD
9. Misalignment of international regulatory bodies.

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. It is therefore crucial that patients can trust the producers of their medicine. The approach to quality management in the pharmaceutical industry has to change. And the industry should see the advantages that other industries have enjoyed for years of developing much more advanced and cost-effective quality techniques. 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. For the pharmaceutical industry, Quality by Design is not only about adjusting to a new set of requirements it is an opportunity to import modern quality management techniques and use them for more cost-effective manufacturing and quality management. The Quality by design (QbD) is a best approach to encourage and support quality and to increase the further thinking about the best ways. Modern quality system would be critical to support QbD and continuous improvement of pharmaceutical products over their lifecycle. Quality by design is an essential part of the modern reliable concept and is an innovative approach towards the pharmaceutical quality. 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 models. Analytical method development and validation by QbD plays a key role in the pharmaceutical industry for ensuring the product quality. The outcome of AQbD 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. The overall advantage of the approach is improved method proficiency, reduced variability, less trials hence less method cost and reduced time consumption, knowledge about the extreme limitations of the method which when traversed may lead to method failures and at times method alternatives.

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REFERENCES

1. Q9: Quality Risk Management. ICH Harmonized Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.
2. Q10: Pharmaceutical Quality System, ICH Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2007.
3. FDA Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool (Draft Guidance).
4. Q8 (R1): Pharmaceutical Development, Revision 1, ICH Harmonized Tripartite Guidelines, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2007.
5. Food and Drug Administration CDER. Guidance for industry: Changes to an approved NDA or ANDA, 2004.

6. Juran J.M., Juran on Quality by Design: The New Steps for Planning Quality into Goods and Services, Simon and Schuster Adult Publishing group, New York, 1991.
7. Food and Drug Administration. Final report on pharmaceutical cGMP for the 21st Century - A risk-based approach. Available at http://www.fda.gov/downloads/ Drugs/Development Approval Process/Manufacturing/ Questions and Answers on Current Good Manufacturing Practices cGMP for Drugs/UCM176374.pdf (Accessed January 28, 2014).
8. Charoo N.A, Shamsher A.A., Zidan, A.S., Rahman Z. Quality by design approach for formulation development: A case study of dispersible tablets, International Journal of Pharmaceutics,2012, 423, 167– 178.
9. Thorat S.R., Meshram S.M., Review on Quality by Designing for Metered Dose Inhaler Product Development, Scholars Academic Journal of Pharmacy, 2015, 4(6), 324-330.
10. Gawade A., Chemate S., Kuchekar A., Pharmaceutical Quality by Design: A New Approach in Product Development, Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences, 2013, 2(3), 5-12.
11. Roy S., Quality by design: A holistic concept of building quality in pharmaceuticals, International Journal of Pharmacy and Biomedical Research, 2012, 3(2), 100-108.
12. Kumar N. et.al. A Review on quality by design approach (QBD) for Pharmaceuticals. Int. J. Drug Dev. & Res.2015; 7:35-44.
13. Innovation and continuous improvement in pharmaceutical manufacturing pharmaceutical CGMPsforthe21stCentury,U.S.FoodandDrugAdministration,2004,URL:http://www.fda.gov/cder/gmp/gmp2004/manufSciWP.pdf
14. U.S. Department of Health and Human Services Food and Drug Administration 2004; Pharmaceutical GMP for the 21stCentury a Risk-Based Approach: Second Progress Report And Implementation Plan
15. Nasr, N. Risk Based CMC Review Paradigm. Advisory Committee for Pharmaceutical Science Meeting 2004; 2: 20-21.
16. Rane S, Bhat D, QbD approach to analytical RP HPLC method development and its validation, International journal of Pharmacy and Pharmaceutical Sciences, 2011;3(1): 179-187.
17. USFDA, Pharmaceutical cGMP for the 21st Century - A Risk-Based Approach: Second Progress Report and Implementation Plan Introduction, Food and Drug Administration, Rockville, MD, 2003.
18. USFDA, Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, Food and Drug Administration, Rockville, MD, 2004.
19. USFDA, Pharmaceutical cGMP for the 21st Century - A Risk-Based Approach: Final Report, Food and Drug Administration, Rockville, MD, 2004.
20. EMA,http://www.emea.europa.eu/docs/en_GB/document_library/Report/2009/10/WC500004903.pdf
21. EMAUSFDA,http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/03/WC500103621.pdf
22. Food and Drug Administration CDER. Guidance for industry: Immediate release solid oral dosage forms scaleup and post approval changes: Chemistry, manufacturing, and controls, in vitro dissolution testing, and in vivo bioequivalence documentation; 1995.
23. Food and Drug Administration CDER. Guidance for industry: Modified release solid oral dosage forms scaleup and post approval changes: Chemistry, manufacturing, and controls, invitro dissolution testing, and in vivo bioequivalence documentation; 1997.
24. Bhagyesh Trivedi. International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(1): 17-29.
25. N.V.V.S.S. Raman, Useni Reddy Mallu and Hanimi Reddy Bapatu. Analytical quality by design (AQbD) approach to test method development and validation in drug substance manufacturing.

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