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REVIEW

Quality by design approach: Regulatory need

Jaiprakash N. Sangshetti [a], Mrinmayee Deshpande [a], Zahid Zaheer [a], Devanand B. Shinde [b], Rohidas Arote [c,*]

[a] *Y. B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Rauza Baugh, Aurangabad 431001, India*
[b] *Department of Chemical Technology, Dr. B. A. M. University, Aurangabad 431004, India*
[c] *Department of Molecular Genetics, School of Dentistry, Seoul National University, Seoul, Republic of Korea*

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Design of experiment;
Risk assessment

Abstract In this era of competition quality has been given prime magnitude; failure to meet such quality allied goals produces massive shift of company in share of market. In this context pharmaceutical industry is utmost regulated industry as it is governed by authoritative regulatory bodies. "Quality could be planned and most of quality deficit arises in the way process is planned and developed", this thought of well known quality expert Joseph Moses Juran gives foundation to the concept of quality by design (QbD). USFDA launched a pilot programme in 2005 to permit participating firms a prospect to submit chemistry, manufacturing, and controls (CMC) of NDA information representing application of QbD. Now USFDA is accelerating QbD drive by making warning to generic manufacturers from January 2013. QbD has its perspectives to contribute the drug design, development, and manufacture of high-quality drug products. In the present review basic consideration of the QbD approach, its historical background, and regulatory needs are discussed. In detail explanation of elements of QbD i.e. method intent, design of experiment, and risk assessment is given. Application of QbD to pharmaceutical and biopharmaceutical processes, development and unit operation associated with it are briefly mentioned. Detail account of QbD to analytical technique is explained thoroughly by referencing examples.

Contents

* Corresponding author. Tel.: +82 2 740 8770; fax: +82 2 745 8483.
E-mail address: rohi06@snu.ac.kr (R. Arote).
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1. Introduction

Quality has been given an importance by all regulatory bodies for pharmaceutical products. Quality means customer satisfaction in terms of service, product, and process. Many of these quality related activities reflect need for companies to excel in global competition. Customer demands the perfection in quality, reliability, low cost and timely performance. Customer satisfaction can be achieved by two ways i.e. features and free from deficiencies in goods. The features like performance, trustworthiness, robustness, ease of use, and serviceability have to built in the product and such product should be free from deficiencies. Quality, productivity, cost, cycle time and value are interrelated terms. Quality activities must try to detect quality problems early enough to permit actions without requiring compromise in cost, schedule or quality. The emphasis must be on precaution rather than on just correction of quality problems. Quality can be the driving force to empower results in other parameters. Hence the quality has to be built in the product as well as services through proper planning, so that the forth coming failure can be avoided. Mere analysis of final product will not work but the quality should be designed in the product. The concept of quality by design was summarized by a well known quality expert Joseph Moses Juran; he believed that quality could be planned and that most quality associated problems have their origin in the way which quality was planned in the first place. The principles of QbD have been used to advance the product and process quality in every industry. Because of need of potent drug with safety profile, pharmaceutical industries are investing billions of money in the drug discovery and development process with endeavour to design quality product and that to with consistency in manufacturing process to deliver the intended performance of product. The information and knowledge gained from pharmaceutical studies and manufacturing provide a base for scientific understanding to support establishment of design space, specification and manufacturing control. Information from pharmaceutical development studies can be a root for quality risk management. Lifecycle management allows making changes in formulation and manufacturing processes during development and providing additional opportunities to gain added knowledge and it further supports establishment of the design space. Design space is planned by the applicant and will undergo regulatory assessment and approval. Working within the design space is not considered as a change. But an operation out of the design space is considered to be a change and has to face a regulatory post approval change process. During the drug development process, the aspects like drug substances, excipients, container closure systems, manufacturing processes and quality control tests are critical to product quality. Critical formulation attributes and process parameters are generally identified and controlled to the extent of assurance of quality which is also an important task. This scientific and knowledge rich understanding will help industry to manufacture quality products and ultimately flourish industry by means of fame as well as financial assets.

2. Historical background

In 2007 FDA received an ~5000 supplements, it was actually a striking raise in the number of manufacturing supplements to applications of New Drug Applications (NDAs), Biological License Applications (BLAs) and Abbreviated New Drug Applications (ANDA's). FDA recognized that there is an increase in lapse of NDA or ANDA submissions by the firms, large number of a supplemental application for every manufacturing change were received. In both original applications and supplements the data mainly focused was on chemistry. And the least attention was given on other important aspects of the manufacturing, such as engineering, product development. Eventually, the FDA acknowledged that more and more controls were required for drug manufacturing processes for efficient drug product and no doubt for better regulatory decision making. It resulted in more stringent regulatory upbringing. To solve this issue in 2002, the FDA implemented changes through the Pharmaceutical cGMP (good manufacturing practice) for the 21st Century. Expectations were mentioned in Process Analytical Technology (PAT) which is a system for designing, analysing, and controlling manufacturing processes based on understanding science and factors which affect the quality of final product. In 2005 here came the time to implement QbD for more systematic approach and USFDA asked some firms to submit their CMC in QbD format (Patricia, 2007). Question base review (QbR) forms the platform of QbD principle (Aloka and Robert, 2009). Recent interview by Nick (2011) with Lawrence Yu Deputy Director, Science and Chemistry, FDA indicates warning that 2013 is deadline for generics to implement QbD.

3. Regulatory aspects to QbD

3.1. FDA perspective

In 2005 USFDA asked participating firms to submit chemistry manufacturing control (CMC) information demonstrating application of QbD as part of New Drug Application. QbD involves thorough understanding of process; a goal or objective is defined before actual start of process. Design space and real time release risk assessment are other parameters for implementation of QbD. 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 (Patricia, 2007).

QbD ultimately helps to implement Q8 and Q9. 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'.

In nutshell,

- Product quality and performance can be assured by designing efficient manufacturing processes.
- Product and process specifications are based on a scientific understanding of how process factors affect product performance.
- Risk-based regulatory approaches are for scientific understanding and control related process for product quality and performance.
- Related regulatory policies and measures are modified to accommodate the real time scientific knowledge.
- Quality assurance is continuous process.

3.2. ICH guideline and QbD (ICH guideline Q8, 2012; ICH guideline Q10, 2012; ICH guideline Q9, 2012)

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*.

3.3. Regulatory challenges and inspection

According to Anastasia G. Lolas and Anurag S. Rathore ''In a QbD concept, the regulatory burden is less because there are wider ranges and limits based on product and process understanding. Changes within these ranges and limits do not require prior approval''.

Traditionally, inspections have been conducted using the FDA system-based approach and in accordance with CDER's Compliance Program ''Inspection of Licensed Bio-logical Therapeutic Drug Products''. But now query arises that how the inspection will take place in the present scenario where QbD is mandated. During prelicense or preapproval inspections under a QbD concept, the FDA inspection team will assess the implementation and effectiveness of the process design as described in the application and whether knowledge and risk management have been transferred successfully from development to manufacturing. The inspection will evaluate the quality system and its effectiveness regarding consistent product quality, change in control procedures, process improvements, deviation management, and knowledge and risk management during the product lifecycle. Inspection of facility and equipment qualification and maintenance as well as raw material screening and supplier management will be same as it was performed previously. But design, testing, and monitoring programmes that demonstrate robustness and consistency would be highlighted (Anastasia and Anurag, 2012).

4. Basic considerations of QbD

As far as pharmaceutical industry is considered safety of patient and providing a quality product have been given prime importance; and to achieve this target QbD assist it by thorough understanding of process which is the ultimate goal of QbD.

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 analysed.
- It offers robust method or process.
- Business benefits are also driving force to adopt QbD.

Method design concept helps to avoid cost involved with post approval changes (Vince et al. (2011a)).

4.1. Elements of pharmaceutical development

QbD comprises all elements of pharmaceutical development mentioned in the ICH guideline Q8. Pharmaceutical Development section is projected to provide a complete understanding of the product and manufacturing process for reviewers and inspectors. To design a quality product and its manufacturing process to consistently deliver the intended performance of product is the aim of pharmaceutical development. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the specifications, and manufacturing controls (Patricia, 2007).

- Different elements of pharmaceutical development include,
- Defining an objective
- Determination of critical quality attributes (CQA)
- Risk assessment
- Development of experimental design
- Designing and implementing control strategy
- Continuous improvement.

4.1.1. Define an objective

Quality target profile (QTP) forms the basis of QbD, which is in relation to the predefined objective criteria mentioned in the definition of QbD.

As per ICH guideline Q8 R2 the Quality Target Product Profile forms the basis for design and the development of the product. Considerations for the Quality Target Product Profile could include:

- Intended use in clinical setting, route of administration, dosage form, delivery Systems.
- Dosage strength(s), Container closure system.
- Therapeutic moiety release or delivery and attributes affecting, Pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance).
- Drug product quality criteria like sterility, purity, stability and drug release as appropriate for dosage form the intended for marketing.

QbD requires a Target Product Profile; it may be called as Quality Target Product Profile (QTPP) which defines the

expectations in final product. In case of analytical method development it is called as analytical target profile (ATP), it is also called as Target Product Profile (TPP). The TPP can play a central role in the entire drug discovery and development processes like optimization, planning and decision making, and designing of clinical research strategies (Lawrence, 2008). The Target Product Profile (TPP) can be used to design the clinical trials, safety and ADME studies, as well as to design the drug product. The TPP will help to identify critical quality attributes such as potency, purity, bioavailability or Pharmacokinetic profile, shelf-life, and sensory properties (Vince et al. (2011a)).

4.1.2. Determination of critical quality attributes.(CQA)

According to ICH Q8 R2 "A CQA is 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". CQAs are generally linked with the drug substance, excipients, intermediates (in-process materials) and drug product. For example CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability whereas for parentrals they are Sterility and clarity. The CQAs can additionally include properties like particle size distribution, bulk density that affect drug product. Mostly CQAs are derived from the Quality Target Product Profile and/or prior knowledge is used to guide the product and process development and Subsequently CQAs are accessed for risk management.

It is stated in ICH Q9 that in case of Potential drug substance CQAs are used to guide process development. Inclusion and exclusion in list of potential CQAs can be done as knowledge drug substance and process understanding increases. In case of biotechnological/biological products, most of the CQAs of the drug product are associated with the drug substance and thus are a direct result of the design of the drug substance or its manufacturing process. Impurities are an important class of potential drug substance CQAs. A quality attribute that must be controlled within predefined limits to ensure that the product meets its intended safety, efficacy, stability and performance. It means all the factors which affect final quality and safety should be controlled.

Dissolution test is crucial for a controlled release drug product and on other hand dissolution test for an immediate release drug product which belongs to the high aqueous solubility and high permeability i.e. BCS class I drug will not prove as critical attribute for quality control viewpoint (Vince et al. (2011a)). CQA differs for type process, dosage form, and type of method development hence thorough knowledge of real time data to working scientists is important.

4.1.3. Risk assessment

It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. Risk assessment helps to increase quality of method or process. Also it is determinant for effect of input variable on method or processes. From risk assessment one can recognize critical attributes that are going to affect final quality of product. A risk assessment is helpful for effective communication between FDA and industry, research/development and manufacturing and among multiple manufacturing sites within company (Patricia, 2007). There may be risk and uncertainty in validation of bioanalytical method though the guidelines for validation are given by various regulatory bodies there may be a variation in interpretation of those guidelines and hence in experimental method designing which leads to unfit method development for intended purpose (Rozet et al., 2010). Risk management for excipients to determine shelf life can be done by statistical parameters (Harry and Lanju, 2012).

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.

Risk management is joint responsibility of quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical department.

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.

ICH guideline Q9 gives description of risk management and various terminologies associated with it, like Risk Acceptance, Risk Analysis, Risk Assessment, Risk Communication, Risk Control, Risk Evaluation, Risk Identification, and Risk Management. Quality management policies should mention procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk. Risk Reduction is actions taken to lessen the probability of occurrence of harm and the severity of that harm.

4.1.4. 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. (Lawrence, 2008) Risk assessment can guide to understand linkage and effect of process parameters and material attributes on product, and ranges for variables within which consistent quality can be achieved. These parameters or attributes are selected for addition in the design space. Information regarding reason for inclusion of some variables in design space as well as exclusion of other variable has to be mentioned. 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. For example impact of excipient variability on particle size distribution, blend segregation propensity can be included in experimental design (Joseph et al., 2011). Gel was prepared using QbD approach, the design space used was developed by a D-optimal design from a total of 15 gel batches, with five factors ethanol, water, carbomer, acid neutralized fraction, and reactor temperature (Juan et al., 2011a,b). 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 (Ivan et al., 2012).

4.1.5. 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 (Lawrence et al., 2009). QbD gives trace on reproducibility and robustness. Process capability index expresses reproducibility of process.

$$\text{Process capability index}(C_pK) = \frac{\text{upper limit of specification} - \text{lower limit of specification}}{6\text{standard deviation}} \quad (1)$$

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 (see Fig. 1). 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 (Lawrence et al., 2009). Control strategy involves but not limited to – control on excipients, drug substance, packaging materials (inputs), specifications, operational control like drying downstream processing dissolution etc.., real time testing or in process testing, finished product testing at regular intervals.

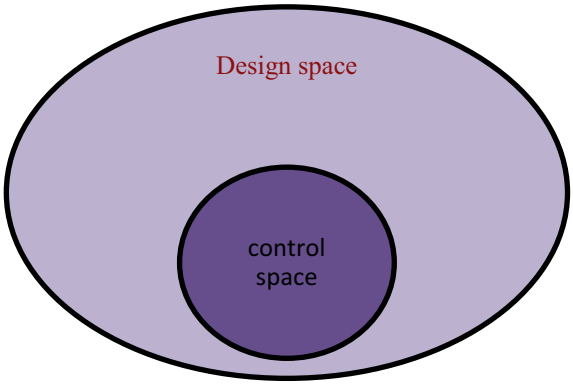

Figure 1 Control space within the design space.

4.1.6. Continuous improvement throughout product life cycle

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. Periodic maintenance can be done within a company's own internal quality system; but design space should be unchanged. The QbD approach avails the continuous improvement throughout products' life cycle this is distinguishing point from the conventional method which is much frozen process.

5. 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. Factors which improve robustness are taken into consideration for the development of analytical method in QbD environment. This approach facilitates continuous improvement in method. Parallel opportunities of application of QbD to analytical method as that of manufacturing process are available in the literature (Mark et al., 2010). It suggests that approaches like target profile, CQA, design space, and risk assessment are applicable to analytical method also. 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 (Mark et al., 2010. 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 (Frederick and Alireza, 2011).

Potential benefits of adopting QbD for analytical method

- The developed method will be more robust which gives greater level of confidence in case of variations in conditions.
- This approach gives greater transfer success when method is transferred from research level to quality control department.
- It provides a space for invention of new techniques by continuous improvement throughout life cycle.
- It helps for enhanced understanding of the method.
- Design space concept avoids the post-approval changes which may cause to pay a high cost for any of the firm.
- It provides greater compliance with regulatory authorities (Mark et al., 2010; Phil et al., 2007).

5.1. Aspects of application of QbD to analytical method

Various aspects explained in pharmaceutical development are also put into practice for development of analytical method in QbD paradigm. Some key aspects are discussed hereunder.

5.1.1. Analytical target profile (ATP)

"QbD is a systematic approach to product and process design and development," (Patricia, 2007). Hence it begins with determination of goal or method intent. In this emphasis is given on the product and process understanding (Mark et al., 2010). ATP is way for method development or it is simply a tool for method development. It describes the method requirements which are expected to be measured. In general the goal of the chromatographic method is separation, quantification and identification of drug substance, impurity or degradents. Impurity is considered to be the critical quality attribute (CQA) (Peter and Bernard, 2008). 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 (Yan et al., 2012). The method requirements will be the accuracy precision, robustness, ruggedness and so on as described in ICH guideline (Phil et al., 2007). Whether it is a conventional method or QbD method detailed information of compound should be collected like its solubility, p^{ka}, p^{H}, UV chromophore, and stability. Yan et al. (2012) stringent method goals can be set to obtain a best method. It provides framework to method development which helps for further planning. It decides what to be measured and within what limit it is required to be measured. ATP is in complete accordance with ICH guideline.

5.1.2. 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 this use of various flowcharts decision tree can be made for correct implementation. In case of HPLC method development scouting is done. In this large number of experimental conditions were tried (p^{H}, temperature, columns, and buffers) (Devesh and Smita, 2011). 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 (Frederick and Alireza, 2011). 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. For example, to determine impurities, HPLC with detector like PDA can be used. In method design, method that meets method requirement is established. Method design may be repeated or modified as and when required throughout the life cycle. Thorough understanding of design intent will form a better Method design. Method design should be done according to standardized approach. This approach helps in method transfer step from research to quality control department. Method development strategy (MDS) includes design of experiments (DoE) (Frederick and Alireza, 2011). It is helpful in risk assessment by gaining knowledge about existing method and allows for effective control strategies for critical parameter. K.E. Monks and et al. present a novel approach to applying Quality by Design (QbD) principles to the development of high pressure reversed phase liquid chromatography (HPLC) methods. They developed a good, robust method for the separation of nine model compounds of pharmaceutical interest in a multidimensional space comprised of four critical parameters: gradient time, temperature, pH of eluent and stationary phase. The criteria of separation success are maximum resolution, maximum robust tolerance windows and minimum run time. In this paper three dimensional experimental designs for optimization of method are given (Monks et al., 2011). Method design is made considering the ICH guidelines for validation hence validation remains formality.

Various experimental design methods are mentioned in the literature. An experimental design is an experimental set-up to 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 (Bieke and Yvan, 2011).

5.1.3. Critical quality attributes (CQA)

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 efficacy can be achieved by demonstrating measurable control of quality attributes i.e. product

specification, intermediate specification, and process control (Mark et al., 2010).

5.1.4. Risk assessment

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 (Patricia, 2007. 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. Risk based approach is based on the ICH guideline Q8 and Q9. 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. The other factors known as risks during the risk assessment can be tested by ruggedness studies, or, to by tested robustness studies. Method which is insensitive to small variations in parameters like instrument settings is robust, whereas a rugged method is one that can bear any noise likely to be encountered during use. The risk assessment approach differs from the older non-QbD approach. Each and every step starting from sample preparation including dilution, extraction is analysed for possible risk involved in it. A fishbone diagram is divided into categories like instrumentation, materials, methods, measurements, laboratory climate, and human factors. Once the risk is assessed it is grouped into three categories.

1. High-risk factors that should be stringently controlled, typical high-risk factors that can be fixed at the time of method development that includes data analysis methods and sample preparation methods.
2. Potential noise factors,
3. Factors that can be explored experimentally to determine acceptable ranges.

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 (Frederick and Alireza, 2011).

5.1.5. 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 (Lukas et al., 2010; Phil et al., 2007). Design Qualification

1. Installation Qualification
2. Operational Qualification
3. Performance Qualification

Considering user requirement specifications (URS), design and technical specification of an instrument are defined, it is part of DQ. As HPLC is commercial-off-the-shelf system in this case the users should make sure that the instrument is suitable for their desired applications. User must confirm that the installation site fulfill all vendor-specified environmental requirements. Here IQ part begins. Equipment is assembled at the user's site and checked for proper working of all the assembled parts.

The combined parameters for operational qualification and performance qualification are given below in Table 1:

5.1.6. Control strategy

It is important that set method performs as intended and consistently gives accurate results, for that purpose control on method is required. A factor identified to have risk has to be controlled. More attention is given to the high risk factors. System suitability can be checked and verified time to time by having control over it (Phil et al., 2007). On ground of practical example; the risk assessment can also help identify a specific control strategy. For example, during robustness studies for an Atomoxetine hydrochloride HPLC impurity profile method, it was found that resolution of the impurities of interest followed the same trend when method parameters such as *n*-propanol and temperature were varied. As a result, an early eluting impurity pair was chosen for system suitability and became a convenient method control strategy because the two

Table 1 Combined parameters for operational qualification and performance qualification.

Module	Parameter
Injector	Precision of injection volume Linearity of injection volume Injection carryover
Autosampler	Thermostatting precision
Solvent delivery system	Flow rate accuracy Mobile phase proportioning Flow rate precision
Detector	Wavelength accuracy Noise Drift Linearity of detector response
Column oven	Thermostatting precision of column oven

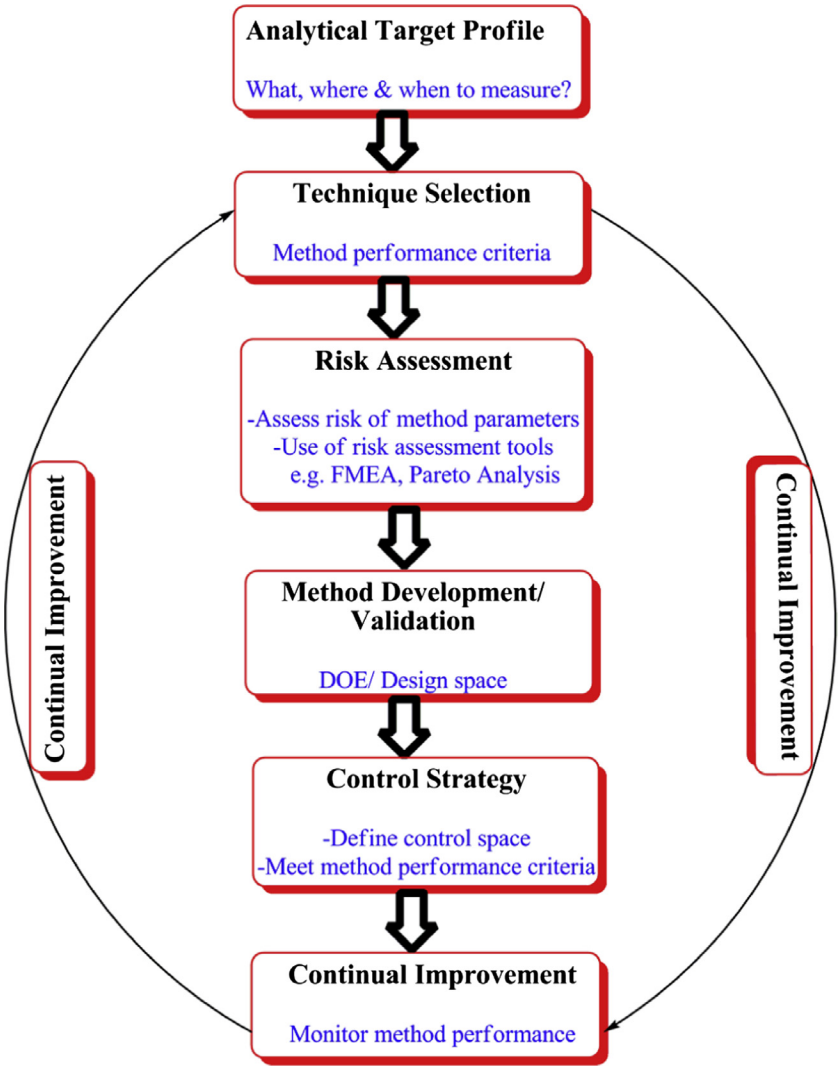

Figure 2 Analytical method development in QbD.

compounds involved were easily obtained (Peter and Bernard, 2008; Frederick and Alireza, 2011). Validation remains the formality it is done in similar way to that of traditional method development in validation (ICHQ2) but in traditional approach method validated after development i.e. it is like checkbox tool, and in QbD the validation parameter in ICHQ2 are consider as method intent.

5.1.7. Life cycle approach

Life cycle approach differs from that of the traditional approach of method development. According to Morefield it includes continuous improvement of method performance and the design space allow flexibility for Continuous improvement in analytical method can be done without prior regulatory approval because of design space made previously (Mark et al., 2010). Knowledge gained from risk assessment and data collected from design of experiments can be used as the repository of knowledge to make justified changes wherever required. A complete process analytical method development in QbD environment is summarized in the following flow chart (see Fig. 2).

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

6.1. For chromatographic technique

6.1.1. In determination of impurity

Gavin gives a quality by design approach to impurity method development for atomoxetine hydrochloride. An ion-pairing HPLC method was developed and associated system suitability parameters for the analysis of atomoxetine hydrochloride are studied. Statistically designed experiments were used to optimize conditions and demonstrate method robustness for the separation of atomoxetine and impurities. Weiyong Li describes a three-step method development/optimization strategy for HPLC assay/impurity methods for pharmaceuticals i.e. multiple-column/mobile phase screening, further optimization of separation by using multiple organic modifiers in the mobile phase, and multiple-factor method optimization using Plackett–Burman experimental designs. Commercially available chromatography optimization software, DryLab was used to perform computer simulations. This approach significantly

reduces the number of runs in method development. When satisfactory separation was obtained, a method optimization is done with Plackett–Burman experimental designs (Weiyong and Henrik, 2003).

Peter et al. (2010a,b) given A QbD with Design-of-Experiments Approach to the Development of a Chromatographic method for the Separation of Impurities in Vancomycin using specialized software with UPLC® Technology. Traditional HPLC gradient methods have capability to separate out 13 of these impurities, while the use of QbD approach with sub-2-pm ACQUITY UPLC Column separation of as many as 26 impurities could be possible.

6.1.2. In screening of column used for chromatography

Connie et al. (2009) describes the particulars of the experimental design, evaluation criteria used and some of the most commonly used analytical columns from reputed column manufacturers. A systematic approach is used to evaluate seven RP-HPLC columns against predefined performance criteria. This approach is a fundamental part of a QbD method development. The data generated for commonly used columns provide help to practicing analyst to meet challenge of developing robust and rugged methods for use in a QbD environment. Recently better selection of column has been explored in UPLC using quality by design (Kormány et al., 2013).

6.1.3. In development of HPLC method for drug products/substances

Monks et al. (2011) presents a novel approach to applying quality by design (QbD) principles to the development of high pressure reversed phase liquid chromatography (HPLC) methods. Four common critical parameters in HPLC – gradient time, temperature, pH of the aqueous eluent, and stationary phase are evaluated within the quality by design framework by the means of computer modelling software and a column database. David et al. (2012) worked on Application of quality by design elements for the development and optimization of an analytical method for protamine sulphate. A robust method was developed. A Box–Behnken experimental design with response surface methodology was then utilized to evaluate the main, interaction, and quadratic effects of these three factors on the selected responses. Method requirements applied to the optimized conditions predicted peak resolutions between 1.99 and 3.61 and tailing factor between 1.02 and 1.45 for the four peptide peaks of protamine sulphate (David et al., 2012).

6.1.4. In capillary electrophoresis

Yi-Hui et al. (2007) worked on Experimental design and capillary electrophoresis for simultaneous analysis of arbutin, kojic acid and hydroquinone in cosmetics. Statistical parameters were used to optimize method.

6.1.5. In stability studies

Karmarkar et al. (2011) reported an application of quality by design (QbD) concepts to the development of a stability indicating HPLC method for a complex pain management drug product containing drug substance, two preservatives, and their degradants are described. The initial method lacked any resolution in drug degradant and preservative oxidative degradant peaks, and peaks for preservative and another drug degradant. The method optimization was done using Fusion AE™ software that follows a DOE approach. The QbD based method development enabled in developing a design space and operating space with particulars of all method performance characteristics and limitations and method robustness within the operating space.

6.1.6. In UHPLC

Szabolcs et al. (2009) developed Rapid high performance liquid chromatography with high prediction accuracy, with design space computer modelling, which demonstrates the accuracy of retention time prediction at high pressure (enhanced flow-rate) and shows that the computer-assisted simulation can be useful with enough precision for UHPLC applications.

6.2. For hyphenated technique

6.2.1. In LC–MS method development

Joseph Turpin gives the QbD approach to liquid chromatographic method development. The article is divided in three parts which includes current approaches to column screening in terms of experimental region, knowledge space, design space coverage, data treatments to quantitation of the column screening experiment, and quantitative method robustness estimation. Parameters are classified in two types depending upon their influence on separation; (1) Primary effectors of separation are column type (column screening), pH, organic solvent type, and Gradient Time (Controls Slope) (2) Secondary effectors of separation are pump flow, gradient conditions, temperature, and ion pairing agent (Joseph, 2012; Peter et al., 2010a,b).

6.3. In bioanalytical method development

Torrealday et al. (2003) developed a HPLC-fluorimetric bioanalytical method for quantitation telmisartan in urine using Experimental design approach for the optimization chromatographic variables that had influence on the fluorescent response. Two designs were applied to fractional factorial design, to evaluate which of the studied variables had an influence on the response, and the central composite design to obtain the response surface from which the optimal conditions for the target response could be deduced.

6.4. In dissolution studies

Miroslav et al. (2010) developed HPLC method for digoxin quantification in dissolution samples in this the experimental design is used to demonstrate the robustness. Effect of minor changes in acetonitrile fraction, flow rate of the mobile phase, column temperature and column length on the characteristics of the digoxin peak are found using full factorial design (2^4). Presented HPLC method was applied in quality and stability testing of digoxin. Jun et al. (2011) worked on quality by design approach to investigate tablet dissolution shift upon accelerated stability by multivariate methods. And presented article on quality by design case study: An integrated multivariate approach to drug product and process development.

6.5. For spectroscopic measurements

6.5.1. In handling complex spectroscopic data

Zengping et al. (2011) in his review focused on Process analytical technologies and real time process control of some spectroscopic issues and challenges for purpose of process understanding. Process analytical technologies (PAT) are more and more being discover and adopted by pharmaceutical and biotechnology companies. To reach this goal there is a need to extract the detail information, and gain knowledge from complex spectroscopic data. A number of new approaches are shown to overcome the limitations of existing calibration/modelling methodologies and describe a practical system which would improve robustness of the process control system and overall control strategy.

6.5.2. In mass spectroscopy

Lianming and Frederick (2012) in their review of recent advances in mass spectrometric methods for gas-phase chiral analysis of pharmaceutical and biological compounds explain Practical projection and existing challenges in quantitative chiral MS techniques for QbD (Quality-by-Design) based pharmaceutical applications.

6.5.3. In near infrared

Mark (2011) has presented a review on Quality-by-Design (QbD) Approach to Quantitative Near-Infrared Continuous Pharmaceutical Manufacturing. Krause (2009) in his review on QbD for Analytical Methods describes elements of QbD principle in relation with analytical methods.

7. Other applications of QbD or elements of QbD

QbD has been applied to pharmaceutical, biopharmaceutical, clinical, and genetics. Some examples where QbD is applied are mentioned hereunder.

7.1. Pharmaceuticals

The delivery of medicine at the appropriate purity, potency, and delivery rate, is expected from the pharmaceutical products. While pharmaceutical regulations have undoubtedly protected the human beings from any of unwanted harms which occurred early in the twentieth century. Hence recent guidelines in Q8 for pharmaceutical development are milestone in the way of making quality products. Application of QbD to various pharmaceutical dosage forms reported in the literature are explained below,

7.1.1. In modified release products

André et al. (2011) in his review of Pharmaceutical Equivalence by Design for Generic Drugs: Modified-Release Products describes quality by design initiative (QbD) provides an enhanced evaluation of equivalent drug approach by introducing the concept of a Quality Target Product Profile (QTPP). The concept of "pharmaceutical equivalence by design", for modified-release generic drug products is illustrated in this article.

Joseph et al. (2011) studied A Quality-By-Design Study for a Roller Compactor. Immediate Release Tablet is used to examine the impact of inconsistency in excipient material properties on the quality attributes.

7.1.2. In sterile manufacturing

Warren (2009) presented details of the applying quality by design to sterile manufacturing processes.

7.1.3. In solid oral dosage form

Deliang and Yihong (2010) in their article, 'Understanding Drug Properties in Formulation and Process Design of Solid Oral Products', discuss scientific and technical principles associated Product and Process Design and development for pharmaceutical product. This approach is consistent with the basic principle of QbD.

Betterman et al. (2012) given A Tale of Two Drugs: How Using QbD Tools Can Enhance the Development Process. This article explains how Quality Target Product Profile, mapping, and risk assessment tools are used. A case study of comparison of a traditional development approach with a QbD enhanced approach of Tradium and Qbidium is explained.

7.1.4. Contribution of (SEM/EDX) to QbD by investigation of pharmaceutical materials

According to Jennifer et al. (2008) Scanning Electron Microscope (SEM/EDX) and microanalysis are used for the identification and analysis of pharmaceutical materials. Detailed observations and measurement of their microstructures can be done by SEM. Hence it can be used as a PAT tool in multi-disciplinary functions to contribute to QbD for process development and control in pharmaceuticals.

7.1.5. In gel manufacturing

Juan et al. (2011a,b) developed quality by design Approach of a Pharmaceutical Gel Manufacturing Process, by Near Infrared Monitoring of Composition and Physical Parameters gel by using the near infrared spectroscopy (NIRS) technique with multivariate chemometric tools. For this purpose, a D-optimal experimental design having normal operational condition (NOC) was used. McMahon, shares his experience of PAT and QbD in Understanding PAT and QbD. He says that PAT and QbD are only stations on the road to ultimate objective (Terry, 2010).

7.1.6. QbD for ANDAs

Robert et al. (2008) in his review discussed quality by design for generics and gives a summary of the key terminology.

7.1.7. In tableting process

Stephanie (2012) recently optimized the Tableting Process with a quality by design Approach. Critical quality attributes like powder properties and granulation are covered in this article.

Andrew Prpich worked on Drug product modelling predictions for scale-up of tablet film coating. He used two fundamental tablet film coating models in a quality by design (QbD) approach to determine the operating parameters for scale-up of Varenicline IR. Role of Design space fundamental of QbD in scale up is mentioned.

Defne et al. (2013) developed a Quality by design approach for wet granulation in pharmaceutical processing: Assessing models for a priori design and scaling.

Vince et al. (2011b) discussed the current status and prospective of role of quality by design (QbD). Experience of Pfizer with FDA's recent chemistry manufacturing, and controls pilot and implementing QbD in its operations is shared.

Morten et al. (2008) applied quality by design for Spray drying of insulin intended for inhalation.

Recently quality by design approach for formulation development for dispersible tablets has been applied (Naseem et al., 2012).

7.1.8. Impact of genotoxic impurities on process development

A current review on 'Overall impact of the regulatory requirements for genotoxic impurities on the drug development process' discusses analytical assessment of genotoxic impurities and the regulations in the toxicological background for establishing limits. It overall light on genotoxic impurities concerns during the development of new drug substances (Antonio et al., 2011).

7.1.9. In co-precipitation process

Quality-by-Design (QbD) has been applied recently for a dynamic pharmaceutical co-precipitation process (Huiquan et al., 2009, 2011).

7.1.10. Nanosuspension preparation

Sudhir et al. (2009) worked on quality by design approach to understand the process of nanosuspension preparation.

Lynn (2011) says that in mid-1982 their team on a development project used a statistical tool and some approaches for optimization, today it is considered as a quality-by-design (QbD). He has presented a case study in which the project met its objectives and did it in fewer days than expected. The use of DOE resulted in a better understanding of critical parameters in his article of quality by Design Circa 1982.

7.1.11. In analysis of excipients and API

Angie and Patricia (2010) applied QbD to excipient formulation and development.

Anurag and Duncan (2010) presented Managing raw materials in the QbD paradigm, understanding risks. Better process and product understanding are the basic belief of quality by design (QbD). Advanced characterization and risk involved in manufacture of raw materials that are typically used in biotech processes are discussed in this article.

Yong et al. (2011) discussed interdependence of Drug Substance Physical Properties and Corresponding Quality Control Strategy. In quality by design (QbD) concept, active pharmaceutical ingredients (APIs) are considered as a critical component. The overall control strategy to ensure drug product quality is discussed.

7.2. Biopharmaceuticals

QbD has also been applied to biopharmaceuticals. It is a fast growing industry parallel to pharmaceutical. High expectation of regulatory bodies is the one of the reasons for adoption of QbD by industries. Manufacturing of biopharmaceuticals involves number of complex process, Chromatography is also the most important unit operation in downstream processing of biomolecules, many of the times it is the primary step for purification. Hence it is beneficial to apply QbD to biopharmaceutical products. Recently QbD has been successfully applied by determining design space for HPLC method for analysis of water soluble vitamins (Wagdy et al., 2013).

7.2.1. In manufacturing of protein

Alex et al. (2012) reported application of the quality by design approach to the drug substance manufacturing process of An Fc fusion protein. Quality attributes of the product were evaluated for their potential impact on safety and efficacy using risk management tools.

Xiaoming et al. (2012) worked on application of quality by design to formulation and processing of protein liposomes. Quality by design (QbD) principles are used in research work to gain a complete understanding of the preparation of superoxide dismutase (SOD) containing liposome formulations prepared using freeze-and-thaw unilamellar vesicles.

7.2.2. In production and characterization of monoclonal antibody-

A systematic quality by design (QbD) strategy was used to develop and characterize a monoclonal antibody production process (Amit, 2010).

Sheryl et al. (2011) present a systematic approach to biopharmaceutical drug product development using a monoclonal antibody as an example.

7.2.3. For chromatographic technique used for purification

Anurag et al. (2011) give High-throughput tools and approaches for development of process chromatography steps which are used for purification of biotechnology products. Hence separation of the various entities that are present at the microbial fermentation or mammalian cell culture, stages of process development are focused. Contribution of QbD in biopharmaceutical is explained in review of High-throughput process development for biopharmaceutical drug substances by Bhambure et al. (2011).

7.2.4. PAT and QbD for biopharmaceutical

Jarka et al. (2011) presented review on Process analytical technology (PAT) for biopharmaceuticals. He has mentioned that a PAT forms a part of the quality by design (QbD) concept which provides tools to facilitate the quality. According to him number of analytical methodologies and tools referred as PAT tools are also useful for QbD.

7.2.5. In nanomedicine

Enikő et al. (2010) worked on rational development of a stable liquid formulation for nanomedicine products. In this work some of the key steps that must be taken for the implementation of "Quality by Design" (QbD) approach for a biotech product are used.

7.2.6. Challenges and solution for application of QbD to biopharmaceutical

Anurag (2010) explains that manufacturing of biotech products involves the number of complex steps, hence there exist number of quality attributes to control, in his article Quality by Design for biotechnology products: challenges and solutions.

7.3. Clinical

Steven et al. (2010) in his work explained the Relationship between Processes Critical Control Parameters and clinical performance of theophylline extended-release tablets.

According to Cook (2012) it may be possible to establish relationships between CQAs and pharmacokinetic parameters in healthy volunteer trials and then also to establish relation-

ships between pharmacokinetics and safety and efficacy. But cost involved does not make it feasible.

7.4. Genetics

Mariana Landin used Design space as an element of QbD in the development of direct compression formulations by gene expression programming' (Landin et al., 2012).

8. Problems in adoption of QbD

Daniel (2011) feels that outsourcing has ruin PAT and QbD. PAT and QbD require collection of data, to act on that, and capitalize indicators and parameters but when a company does not own the equipment, it is often difficult to implement. There may be confusion where to adopt QbD and why? FDA has recommended it should be adopted in Phase II but it is worth at any point, at Phase II development studies are at peak so design space can be developed. Many other questions are discussed with officials from US FDA administration office for new drug quality assessment and office compliance by Angie (2009).

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.

9. Conclusion

QbD has gain importance in the area of pharmaceutical processes like drug development, formulations, analytical method and biopharmaceuticals. The main reason behind adoption of QbD is the regulatory requirements. Pharmaceutical industry needs a regulatory compliance so as to get their product approved for marketing. Nevertheless QbD approach gives quality product with cost effective procedures and that is the basic need. QbD replaces previously used frizzed approach of process development by providing a design space concept. Moving within design space would not require post approval changes thereby reducing the cost involved . QbD approach to generic drug products from January 2013 is recommended. It is ultimately helpful to regulatory bodies for inspection and review process but it will avoid loss raised due to hurry and unethical struggle of private firms to market their product as early as possible, because QbD involves thorough understanding of process through science and risk based approach.

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