CHAPTER 1

OVERVIEW OF QbD

1.1 INTRODUCTION

Quality of product is of utmost important in pharmaceutical manufacturing. FDA continually sets certain standards to obtain quality medicines to the patients. They also try to identify ways to encourage manufacturers to improve manufacturing processes to ensure consistent product quality throughout the product's life cycle. The quality is main concern for any manufacturing process because of its direct impact on patient's health. The economic growth of any company also depends on quality of product.

In pharmaceutical products, the quality is the function of drug substance, excipients, manufacturing and packaging processes. If we want desired quality in the final product, it must be built into the product. To ensure this, we require thorough understanding of how material attributes, process parameters and formulation parameters influence product quality.

The main need of any product development is to obtain a quality product which can fulfill patients need. So in pharmaceutical development process, the final products should be designed as such to meet patients' needs and to achieve intended product performance. There are various steps involved in development of product in which strategies are differing from company to company and from product to product. Up to date, the focus of researchers is to obtain quality product, whatever the approach and scope of development may be. On that basis, the researchers might choose either everyday approach (conventional) or a more systematic approach (advanced) or combination of both for product development. Now a days, FDA announced that every product development file must have Quality by Design (QbD) approach.[1]

In order to describe QbD, we must first define what we mean by quality. Janet Woodcock (Director for the Centre for Drug Evaluation and Research) defined pharmaceutical quality as a 'product that is free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer'.[2] Also 'quality in manufacturing is a measure of excellence or a state of being free from defects, deficiencies, and significant variation'.

According to ICH Q8 guideline, QbD is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on

sound science and quality risk management. [3] As QbD says more systematic approach to development, it can include combination of prior knowledge, design of experiments (DOE), quality risk management, and knowledge management (ICH Q10) throughout the product life cycle. When implementation of such systematic approach is carried out, improvement happens in the desired quality of the product and helps the regulators to better understand a company's strategy.

QbD was first described by well-known quality expert Joseph M. Juran.[4] Juran believed that quality could be planned, so that most quality crises and problems relate to quality will be diminished. His discovery of "designed in" concept is used in QbD for optimization of process/product. As per this concept, the quality attribute should be identified and designed through systematic implementation of an optimization strategy.

The foundation of QbD is to identify characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics. In order to do this the relationships between formulation and manufacturing process variables (including drug substance and excipient attributes and process parameters) and product characteristics are established and sources of variability identified. This knowledge is then used to implement a flexible and robust manufacturing process that we can adapt and produce a consistent product over time.[5]

Implementation of QbD is complex and challenging work in pharmaceutical industry. Many of the concepts, frameworks (agendas) and tools are new to pharma practitioners. Although it is implemented well, there is lot of confusion among practitioners about the use of QbD tools. QbD brought a shift in industry paradigm to move away from dependence on testing for quality to building quality into the design of the product and processes. This should in turn bring about a more scientific, technological and risk based approach.

The main objectives of Quality by Design

- To facilitate innovation and continuous improvement throughout the product lifecycle
- To achieve meaningful product quality specifications that are based on clinical performance
- To provide regulatory flexibility for specification setting and post-approval changes
- To increase process capability and reduce product variability and defects by enhancing product and process design, understanding, and control

- To increase product development and manufacturing efficiencies
- To enhance root cause analysis and postapproval change management
- To streamline the submission and review processes

Table 1.1| Current state vs. Desired QbD state

Aspect	Current state	Desired QbD state
Pharmaceutical development	Empirical; typically univariate experiments (Observed with single variable at a time)	Systematic; multivariate experiments (Well organized with multiple variables)
Manufacturing process	Locked down; validation on three batches; focus on reproducibility	Adjustable within design space; continuous verification within design space; focus on control strategy
Process control	In-process testing for go/no-go; offline analysis	PAT utilized for feedback and feed forward in real time
Product specification	Primary means of quality control; based on batch data	Part of overall quality control strategy; based on product performance
Control strategy	Mainly by intermediate and end product testing	Risk-based; controls shifted upstream; real-time release
Lifecycle management	Reactive to problems and OOS; postapproval changes needed	Continual improvement enabled within design space

As stated in Table 1.1, FDA recognizes that only increase in testing does not improve product quality, it also requires the systematic design approach. With the help of QbD various costs can be reduced such as testing cost, facility cost and resources cost. These costs are more in case of conventional quality by testing approach compared to QbD.

When considered the use of QbD over conventional method, QbD covers a better scientific understanding of critical process and product qualities. It also covers designing controls and tests based on the scientific limits which come by understanding during the development phase. Also it uses the knowledge obtained during the life-cycle of the product to work on a constant improvement of product.

An important part of QbD is to understand how process and formulation parameters affect the product characteristics (also called critical quality attributes (CQA's)) and subsequent optimization of these parameters should be identified in order to monitor these parameters on-line in the production process. QbD can also facilitate the use of innovative technologies and promote the use of new approaches to perform process validation, such as continuous quality verification.

Finally, QbD is an evolution and not a revolution'' – an evolution that is in response to the increasing cost pressures on both the regulatory agencies and industry to control the increase of drug prices.[6] QbD will continue to evolve for years to come as new tools and technologies advance to improve the way we mitigate risks and increase our understanding and control of the manufacturing processes. In addition to increasing quality, the pharmaceutical industry will reduce development and manufacturing cycle times as well as costs in the process.

1.2 HISTORY OF QbD

In the area of pharmaceutical quality improvement, FDA recognized that more and more controls should be required in the manufacturing processes for efficient drug product and also for better regulatory decision making. It resulted in more stringent regulatory background. On the basis of this, FDA announced proposed amendments to "Current Good Manufacturing Practices" (cGMP) in 2002. According to this, an emphasis was given on establishing a 21st century guide on pharmaceutical manufacturing with a target of development in science and technology. For that there is need of establishing a more systematic science and risk based approach to the development of pharmaceutical products.

FDA released "Guideline on General Principles of Process Validation" in 1987. This guideline emphasize that process validation is complete with the 3 validation lots at the commercial scale. An alternative approach to this traditional process validation is the continuous process verification, also known as life-cycle approach which is the essence of the concept of QbD.

ICH (1999) defines the concept of quality and assists in the establishment of global specifications for new drug substances or drug products.[7]

FDA (2004) outlines the QbD concept and summarizes initiatives to encourage science-based policies and innovation in pharmaceutical development and manufacturing. Proposes risk assessment as a tool to evaluate the impact of variations in process inputs on product quality.[8]

FDA (2004) defines the industrialization process as the set of activities related to product design, process design and technology transfer. It acknowledges the problems in these steps which routinely disrupt or delay development programs.[9]

The initiation of the cGMPs for the 21st Century Initiative and the publication of the Process Analytical Technology (PAT) guidance in 2004 by the FDA construct the way for the modernization of the pharmaceutical industry. According to guidance, PAT is a system for designing, analyzing, and controlling manufacturing processes based on understanding of science and factors which affect the quality of final product. Also PAT is a

framework for innovative pharmaceutical development, manufacturing and quality assurance.[10]

Finally in 2005, the time came to implement QbD for more systematic approach and USFDA asked some firms to submit their chemistry manufacturing control (CMC) in QbD format.[9]QbD involves thorough understanding of process; a goal or objective is defined before actual start of process.

Question based review (QbR) forms the platform of QbD principle.[11] QbR is a general framework, recommended as a submission format by the draft guidance for industry ANDA Submission - Content and Format of Abbreviated New Drug Applications, for a science and risk-based assessment of product quality. It contains important scientific and regulatory review questions related to product and process design and understanding, product performance, and control strategy. The QbR format was fully implemented for assessment of ANDAs in 2007. Revised questions were developed in 2012 and 2014 to better capture quality-by-design (QbD) expectations, incorporating both internal and external stakeholder feedback.

The key framework guidance documents for implementation of QbD are ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management (published in 2005) and ICH Q10 Pharmaceutical Quality System (published in 2008).

- ICH Q8 Pharmaceutical Development focuses on the content of the Module 3.2.P.2 of the Common Technical Document (CTD) and promotes the concept of QbD. Final guideline Q8(R2) was published in 2008. It supports knowledge gained through the lifecycle of a product and using scientific approaches and quality risk management principles.
- ICH Q9 Quality Risk Management defines risk and offers a systematic approach to quality risk management via describing how to conduct risk assessments and to manage the risks. This guidance provides the principles and some of the tools of quality risk management. This guide can also be used as a resource document that is independent of other ICH Quality documents. This guide leads to improvement in existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory framework.
- The ICH Q10 describes a model for an effective pharmaceutical quality system that is based on International Standards Organization (ISO) quality concepts. This includes applicable GMP regulations and complements ICH Q8 and ICH Q9, and is applicable for a lifecycle of a product. This guideline focuses on regulating the quality management systems (QMS) into industry; where by any changes to

manufacturing processes would be managed by appropriate change control procedures have been developed.

- Although the initial focus of the science and risk based agenda was linked primarily to drug product, greater emphasis is now being placed on drug substance with the evolution of ICH Q11 dedicated to the manufacture of drug raw materials. QbD provides unique opportunities to go beyond what was done in the past. The guideline focuses on development and manufacturing process of both chemical and biotechnological/biological drug substances and is intended to provide guidance in the scope of ICH Guideline Q6A and Q6B.
- If the principles described in the ICH Q8, Q9 and Q10 guidance documents are implemented together in a holistic manner, then an effective system that emphasizes a harmonized science and risk-based approach to product development and maintenance is in place. This provides an even greater (quality) assurance that the patient will receive product that meets the CQA's.

Some elements of QbD have been used for many years. For example, the use of design of experiment (DOE) in 1920's as factorial designs were applied in agricultural science, and in the 1950's when they were more widely used for industrial applications. Failure mode effect analysis (FMEA), a commonly used risk assessment tool, was developed by the United States Military to assess equipment and system failures. In the 1990's, software was developed that combined risk assessment and DOE techniques.

The use of QbD strengthened in 2007,when FDA received up to 5000 supplements. It was actually eye-catching rise in the number of manufacturing supplements to applications of New Drug Applications (NDAs), Biological Licence Applications (BLAs) and Abbreviated New Drug Applications (ANDA's). FDA recognized that there is an increase in delay of NDA or ANDA submissions by the firms. So 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 and product development.

1.3 REGULATORY ASPECTS OF QbD

Regulatory authorities, both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) are placing more attention on the QbD component as a part of regulatory filing. QbD has become a crucial part of a drug development process. Regulatory bodies think that, by providing the quality at the design stage will benefit the organizations by reducing the defects or deviations at the later stages of product development. It also

benefits the organizations on reducing the cycle time for the optimized product development.

FDA perspective

According to FDA,

- 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 a continuous process.

Regulatory challenges and inspection

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 Center for drug evaluation and research (CDER's) Compliance Program ''Inspection of Licenced Biological Therapeutic Drug Products''. But now query arises that how the inspection will take place in the present scenario where QbD is mandated. During pre-licence or pre-approval inspection 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.[12]

Regulatory authorities, both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) are placing great emphasis on the QbD component as a part of regulatory filing. QbD has become a crucial element of a stream-lined drug development process. QbD by providing the Quality at the design stage will benefit the organizations by reducing the defects or deviations at the later stages of product development, which prove

to be very expensive. It also benefits the organizations on reducing the cycle time for the optimized product development.

A greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application. It is the knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science and risk-based submissions and regulatory evaluations. Nevertheless, appropriate data demonstrating that this knowledge is based on sound scientific principles should be presented with each application.

Chemistry manufacturing control (CMC) reviews procedure: The number of new drug applications (NDAs), investigational new drug applications (INDs), abbreviated new drug application (ANDAs), and Biologics licence application (BLAs) and their supplements containing QbD approaches has increased in the past two years. Because of this increase, the Center recognizes the need for reviewers to consistently implement the ICH guidance's in their reviews. Reviewers should ensure that applications contain at least the minimum information on pharmaceutical development described by ICH Q8(R2) as "At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified." As needed, the reviewer should confer with CMC subject matter experts and members of the extended review team (e.g., medical officer, pharmacology/ toxicology reviewer) to establish the relevance of CMC information that supports the drug's safety, efficacy, and performance.

Applications can include information on enhanced knowledge of the product and process, which can be used to support more flexible regulatory approaches.

- Reviewers should determine whether an application includes sufficient enhanced knowledge that demonstrates the applicant's understanding of material attributes, manufacturing processes, and controls for product quality to support the proposed flexible regulatory approaches. Examples of flexible regulatory approaches are as follows:
    - Manufacturing process improvements without regulatory notification (e.g., movement within a design space).
    - Approaches to reduce post-approval submissions through submission of change protocols (e.g., as described in 21 CFR 314.70(e), 21 CFR 601.12(e) or "Comparability Protocols –

Chemistry, Manufacturing, and Controls Information," Draft, February 2003).
    - In-process tests in lieu of end product testing, including real time release testing approaches (e.g., "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance," September 2004).
    - Mathematical models (e.g., multivariate models) as surrogates for traditional end product testing.
- Reviewers should ensure, in situations when real time release testing is proposed, that the associated methodology is included in the specifications for an attribute that is indirectly controlled (e.g., through in-process testing or surrogate model).

ICH Q9 provides a systematic approach to quality risk management. The risk assessments are usually the basis for the control strategy and those submitted in the application can justify the proposed flexible regulatory approaches.The reviewer should evaluate each risk assessment presented in an application. The reviewer should take a scientific and risk-based approach when reviewing the application:

- The reviewer should evaluate the risks to product quality and the ability of the control strategy to suitably control the risks. The reviewer may choose to conduct an independent formal risk assessment using the tools provided in ICH Q9 to aid with this evaluation.
- The extent of the review should be determined by the importance of the process or material being reviewed and the severity of its potential effect on product quality.
- As outlined in ICH Q10, the manufacturer's quality system is an important part of ensuring continued product quality. The reviewer should collaborate with the investigator and compliance officer, as needed, regarding potential risks in the manufacturing process if potential risks are discovered during the course of the review. This information is helpful during an inspection.

1.4 PHARMACEUTICAL QUALITY BY TESTING

As a traditional approach, the assurance of quality is given by testing at various stages of manufacturing. In that first the raw materials are tested, then the processes and then finally the end product. If a particular batch does not conform to the required specifications, the entire batch is rejected as 'Out of Specification'. This leads to an enormous amount of wastage of industry resources, time and money. Also, any small change in the process requires various permissions from FDA, which is a lengthy process. The product fails

to reach the market when there is demand. This in turn leads to shortage in supply and hike in prices. In this approach, the flexibility in the manufacturing process is highly restricted and more emphasis is on the end-product testing.

As per quality by testing, the product quality is ensured by raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in-process material testing, and end product testing. If they meet the manufacturer's proposed and FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products.[13]

Since a few tablets out of several million are tested, drug manufacturers are usually expected to conduct extensive in-process tests, such as blend uniformity, tablet hardness, etc., to ensure the outcome of product. Manufacturers are not permitted to make changes to the operating parameters specified in the batch record or other process changes without filing supplements with the FDA. As a result, the FDA has been overwhelmed by the number of Chemistry, Manufacturing, and Controls (CMC) supplements filed in recent years. This combination of fixed manufacturing steps and extensive testing is what ensures quality under the traditional system. Limited characterization of variability, inadequate understanding to identify and quantify critical process parameters, and caution on the part of regulators leads to a very rigid and inflexible specifications that prohibit the release of products that may have acceptable clinical performance.[14] Significant industry and FDA resources are spent debating issues related to acceptable variability, need for additional testing controls, and establishment of specification acceptance criteria. Often these debates are concentrated on acceptance limits or statistical aspects.

FDA reviewers' conservatism results from the fact that manufacturers may not understand how drug substance, excipients, and manufacturing processes affect the quality of their products or they do not share this information with FDA reviewers. Under the traditional regulatory evaluation system, all products are treated equally without regard to the risk to the consumer.[15] This has the effect of placing too much review time on low-risk products and more significantly, takes away needed resources from the review of high-risk products. CMC review assessments of complex dosage forms (modified release products, topicals and transdermals) as well as narrow therapeutic index drugs differ only marginally from those of simple dosage forms (many immediate release solid oral products). Further, all CMC information in applications are sometimes evaluated equally, without differentiation of criticality, resulting in the requirement of intensive resources for each application.

In summary, product quality and performance are, in the traditional framework, achieved predominantly by restricting flexibility in the manufacturing process and by end product testing. The present regulatory review system places little or no emphasis on how the design of an effective and efficient manufacturing process can ensure product quality. As a result, the complexities of process scale-up, particularly for complex dosage forms are often not recognized. Product specifications often are derived using test data from one or more batches (often not at production scale), and mechanistic understanding does not play a significant role in this process. Finally, the burdensome regulatory requirement of supplements imposed on manufacturers for executing minor and incremental changes to manufacturing processes and controls inhibits continuous improvement and strategies for the implementation of continuous "real time" assurance of quality.

1.5 ELEMENTS OF QbD

1.5.1 Quality Target Product Profile (QTPP)

Quality Target Product Profile (QTPP) is defined as "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." During development of new drug product, the QTPP could evolve and be refined as the project development process progresses.

A QTPP could be considered a qualitative and quantitative description of the design goal. Strategies, prior knowledge and experience of a process or availability of equipment and facilities could influence the choice of QTPP. The QTPP is specified only for the finished product. Although there is no special format to provide the QTPP information, it would be useful to present in a tabular format in the application. The QTPP will help to identify critical quality attributes such as potency, purity, bioavailability or pharmacokinetic profile, shelf-life, and sensory properties. E.g., the route of administration, dosage forms, bioavailability, strength, and stability. (Table 1.2)

Table 1.2| Quality Target Product Profile (QTPP) for tablets

QTPP Element	Target	Justification
Dosage form	MR Tablet	Pharmaceutical equivalence requirement: same dosage form
Route of administration	Oral	Pharmaceutical equivalence requirement : same route of administration
Dosage strength	10 mg	Pharmaceutical equivalence requirement : same strength

(Continued)

QTPP Element	Target	Justification
Pharmacokinetics	Fasting study and fed study 90% study confidence interval of the PK parameters	Bioequivalence requirements Initial plasma concentration through the first two hours that provides a clinically significant
Area under curve	AUC_{0-2} ,AUC_{2-24} , $AUC_{0-\infty}$, and C_{max} , should fall within bioequivalence limit	Therapeutic effect followed by a sustained plasma concentration that maintains the therapeutic effect
Stability	Atleast 24	Equivalent to or better than reference listed along (RLD) shelf life
Drug product quality attributes	Physical attributes	Pharmaceutical equivalence requirement: meeting the same compendia or other applicable (quality) standards (i.e. identity, assay, purity and quality)
	Identification	
	Assay	
	Content uniformity	
	Degradation products	
	Residual solvent	
	Drug residual	
	Microbial limit	
	Water content	
Container closure system	Suitable container closure system to achieve the target shelf life to ensure tablet integrity during shipping	HDPE bottles with child residence caps are selected based on similarity to the RLD packaging. No further special protection is needed due to the stability of drug substance Z
Administration/ concurrence with labeling	A scored tablet can be divided into two 5 mg tablets	Information is provided in the RLD labeling
	The tablet can be taken without regards to food (no food effect)	
Alternative methods of administration	None	None are listed in the RLD labeling

1.5.2 Critical Material Attributes (CMA)

In identification of CQA's of drug product, the assessment of linkage between drug substance to drug product is necessary. The intended quality of the drug substance should be determined through consideration of its use in the drug product as well as from knowledge and understanding of its physical, chemical, biological, and microbiological properties or characteristics, which can influence the development of the drug product (e.g., the solubility of the drug substance can affect the choice of dosage form).

A clear rationale for why excipient types, grades, and amounts are selected is part of the product understanding. An understanding of which material attributes contribute most to the excipient functionality is important to performance. Supplier specifications may be a poor indicator of excipient functionality in a dosage form and hence may not be critical material attributes. In some cases, it may be necessary to introduce additional testing on incoming materials that are more relevant to how the excipient impacts the dosage form performance.[16]

The selection of the proper salt, solid form (amorphous, polymorph), particle size and morphology, and degree of aggregation will impact critical quality attributes such as solubility, dissolution rate, chemical and physical stability as well as manufacturability (bonding index, stickiness, flow, filterability).

1.5.3 Critical Process Parameters (CPP)

In accordance with ICH Q8 (R2) a critical process parameter is one whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. A pharmaceutical manufacturing process usually consists of a series of unit operations to produce the desired quality product. A unit operation is a discrete activity such as mixing, milling, granulation, drying, compression, or coating that involves physical or chemical changes. CPP's are process inputs that have direct and significant influence on CQA's when they are varied within regular operation range.

The process parameters considered should include the type of equipment and equipment settings, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture, etc.

To demonstrate the reproducibility and consistency of a process, process capability should be studied. Process capability is a statistical measure of the inherent process variability for a given characteristic. The most widely accepted formula for process capability is six sigma. Process capability index

is the value of the tolerance specified for a particular characteristic divided by the process capability, which is defined as follows

ICH Q10 states that in order to ensure a maintained state of control. Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality. The process performance and product quality monitoring system should, for example, use quality risk management in order to establish a control strategy. These controls must encourage an effective CAPA.

Knowledge Management: Product and process knowledge should be managed from development through the commercial life of the product up to product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analyzing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and change management activities.

1.5.4 Identify Critical Quality Attributes, Process Parameters, and Sources of Variability

The identifying potential critical quality attributes (CQAs) of the drug product is essential step in QbD, so that those product characteristics having an impact on product quality can be studied and controlled. Determining the critical quality attributes of the drug substance, excipients etc., and selecting the type and amount of excipients to deliver drug product of the desired quality.

A pharmaceutical manufacturing process is usually comprised of a series of unit operations to produce the desired product. A unit operation is a discrete activity that involves physical changes, such as mixing, milling, granulation, drying, compaction, and coating. A physical, chemical or microbiological properties or characteristics of an input or output material is defined as an attribute. The quality and quantity of drug substance and excipients are considered as attributes of raw materials.

1.5.5 Risk Assessment

Quality Risk Management (QRM, as described in ICH Q9) can be used in a variety of activities including assessing options for the design of the manufacturing process, assessing quality attributes and manufacturing process parameters, and increasing the assurance of routinely achieving acceptable quality results. Risk assessments can be carried out early in the

development process and repeated as greater knowledge and understanding become available. It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g., standard operating procedures). The use of informal risk management processes (using empirical tools or internal procedures) can also be considered acceptable.

QbD provides tools to systematically risk assess all the possible inputs to a process to identify those relatively few that have the greatest potential to impact the process. In risk assessments, especially for the drug product, linkage of input and process variables to CQAs is carried out. Tools used in the risk assessment included the Ishikawa or fishbone diagram, failure mode effect analysis (FMEA), and Pareto analysis. An Ishikawa or fishbone diagram is used to identify all potential variables, such as raw materials, compression parameters, and environmental factors, which can have an impact on a particular CQA, such as tablet hardness. A FMEA can then be used to rank the variables based on risk (i.e., a combination of probability, severity, and detectability) and to select the process parameters with higher risks for further studies to gain greater understanding of their effects on CQAs.

A multidisciplinary team based on prior knowledge and experiments amasses the risk assessment. "It is important to provide a systematic risk analysis of how raw materials, process steps, and process parameters affect product quality," One of the points to consider in risk assessment, is to provide an explanation when citing prior experience as the basis for assigning risk. The risk assessment that leads to the development of a comprehensive control strategy to reduce risk to product quality should be described, and the risk reduction and control should be discussed for changes that occur inside or outside the design space, "Risk assessment can provide increased assurance to quality," because "process variability is identified and its linkage to product CQAs is understood; process and product controls reduce the impact of variability; and quality product will continue to be made when movement within the design space occurs in the future." A risk assessment also is important for effective communication between FDA and industry and for intra company communication (such as between research/development and manufacturing and among multiple manufacturing sites), "And within FDA, risk assessment allows for a dialogue between pre and post-marketing review functions and among review, compliance, and field inspection staffs.

1.5.6 Design of Experiments (DOE)

DOE is defined as "a structured analysis wherein inputs are changed and differences or variations in outputs are measured to determine the magnitude of the effect of each of the inputs or combination of inputs." [17]

It is a structured and organized method to determine the relationship among factors that influence outputs of a process. When DOE is applied to pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness, and friability. As each unit operation has many input and output variables as well as process parameters, it is impossible to experimentally investigate all of them. Scientists have to use prior knowledge and risk management to identify key input and output variables and process parameters to be investigated by DOE.

DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those that do not, as well as details such as the existence of interactions and synergies between factors. Based on the acceptable range of CQAs, the design space of CPPs can be determined. When considering scale-up, however, additional experimental work may be required to confirm that the model generated at the small scale is predictive at the large scale. This is because some critical process parameters are scale dependent while others do not. The operating range of scale dependent critical process parameters will have to change because of scale-up. Prior knowledge can play a very significant role in this regard as most pharmaceutical companies use the same technologies and excipients on a regular basis. Pharmaceutical scientists can often take advantage of past experience to define critical material properties, processing parameters and their operating ranges.[18]

1.5.7 Design Space

ICH Q8 (R1) defines Design Space (DS) as, the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. The Design Space is linked to criticality through the results of risk assessment, which determines the associated CQAs and CPPs.

The design space also contains the proven acceptable ranges (PAR) for CPPs and acceptable values for their associated CQAs. Normal operating ranges are a subset of the design space and are managed under the company's Quality System. Information regarding site and scale of manufacture may also be included, depending on the quality of the process knowledge upon which the design space is based. A design space may be constructed for a single unit operation, multiple unit operations, or for the entire process. Submission of a design space to FDA is a pathway obtaining

the ability to operate within that design space without further regulatory approval.[19]

Some of the steps involved in design space implementation:

- Rational of inclusion of CPP and CMA in design space should be presented.
- In some cases, rational of exclusion of certain parameters can be described.
- Knowledge gained through study should be described.
- Analysis of historical data can be done.
- Operation within design space will result a product meeting defined quality.
- Establish single design space for unit operation or single design space for multiple operations.
- While describing design space, need to consider type of operational flexibility desired.
- The edge of failure for CPP and CMA should be determined.

1.5.8 Control Strategy

Control Strategy is defined as "a planned set of controls, derived from current product and process understanding that assures process performance and product quality". It helps in avoiding defect & maintaining desired quality.[20] The control strategy in the QbD paradigm is established via risk assessment that takes into account the criticality of the CQA and process capability. The control strategy can include the following elements:

- Procedural controls,
- In-process controls,
- Lot release testing,
- Process monitoring,
- Characterization testing,
- Comparability testing, and
- Stability testing.

Development of a Control Strategy requires a structured process, involving a multi-disciplinary team of experts, linking pharmaceutical development to the manufacturing process, and engineering controls of process equipment.

1.5.9 Process Analytical Techniques (PAT)

PAT is defined as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of

critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality."

There are many tools available that enable process understanding for scientific, risk-managed pharmaceutical development, manufacture, and quality assurance. These tools, when used within a system, can provide effective and efficient means for acquiring information to facilitate process understanding, continuous improvement, and development of risk-mitigation strategies. In the PAT framework, these tools can be categorized according to the following:

- Multivariate tools for design, data acquisition and analysis
- Process analyzers
- Process control tools
- Continuous improvement and knowledge management tools

An appropriate combination of some, or all, of these tools may be applicable to a single-unit operation, or to an entire manufacturing process and its quality assurance.

1.5.10 Continuous Improvement

"Continuous Improvement is an essential element in a modern quality system that aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. These efforts are primarily directed towards reducing variability in process and product quality characteristics."

QbD focuses on building quality into the product and manufacturing processes, as well as continuous process improvement – reduction of variability.

The backbone for continuous improvement is the Pharmaceutical Quality System (PQS). PQS should facilitate continual improvement and help to: "Identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill quality needs consistently.

1.6 BENEFITS OF QbD

The QbD can benefit to the industry and to the FDA as follows:

Benefits to industry:

1. Strongly focused on collaboration between research and manufacturing
2. QbD advances process understanding for increased effectiveness and efficiency

3. The "real time, real data" sharing of industry knowledge, fully supports the product life cycle
4. Ensures better design of products with less problems in manufacturing
5. Reduces number of manufacturing supplements required for post market changes rely on process and risk understanding and risk mitigation
6. Allows for implementation of new technology to improve manufacturing without regulatory scrutiny (examination)
7. Allows for possible reduction in overall costs of manufacturing i.e. less waste
8. Ensures less difficulties during review –reduced deficiencies lead quicker approvals
9. Improves interaction with FDA –deal on a science level instead of on a process level
10. Allows for continuous improvements in products and manufacturing process
11. Ensure higher level of assurance of product quality for patient
12. Efficiency and cost saving for industry
13. Increase efficiency of manufacturing process
14. Minimize and eliminate potential compliance action
15. Less validation burden

Benefits for FDA:

1. Enhances scientific base for review
2. Improves information in regulatory submissions
3. Provides better consistency
4. Provides for more flexibility in decision making
5. Ensures decisions made on science and not on empirical information
6. Involves various disciplines in decision making
7. Uses resources to address higher risks
8. The science- and risk-based approach boosts regulator's confidence by minimizing regulator risk
9. Reduces post approval regulatory submissions

The implemented QbD promotes the continuous monitoring of each of the critical unit operation that is predefined, based on scientific rationale. This monitoring ensures the process is in control and also that the required CQA's are achieved. Thus in the long run, this approach can eliminate final QC release testing and save money by constant investigations for OOS events that occur from lab or sampling errors.

Need of QbD:

- It gives higher level of assurance of product quality
- It benefits cost saving and efficiency for industry and regulators
- It facilitate innovation to address unmet medical needs
- It increases efficiency of manufacturing process and reduces manufacturing cost and product rejects
- It minimizes/eliminates potential compliance actions, costly penalties and recalls
- It enhances opportunities for first cycle approval
- It streamlines post approval manufacturing changes and regulatory processes
- It facilitate post approval cGMP inspections
- It give opportunities for continual improvement

QbD approach takes into account patient/customer needs and emphasizes that quality should be built into the product. QbD supports development of Design Space under which the process produces drugs of the desired quality. The QbD approach ensures that we manufacture robust products using sound processes. QbD promises to ultimately contribute to improving the safety of drugs compared to existing practices.

Seven steps of quality by design start up plan[21]

1. Appoint an independent QbD expert
2. Audit your organization and process with the expert conducting a gap analysis
3. Hold a basic quality by design workshop with all your personnel
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"

1.7 CURRENT STATE OF QbD

Most of the major pharma companies are now engaging with QbD, with numerous projects now underway. QbD is being introduced slowly, and shouldn't be used for products already on the market. One new methodology currently being introduced is continuous processing. The first requirement to make a process continuous is to have a proper understanding of the product requirements, and then the critical unit operations. After that point, whether to make a process continuous is a business decision as to whether it fits with the product volume and the facility constraints.

Adopting QbD will increase costs at development but this would be offset by more successful launches, less loss in production, fewer deviations, and fewer recalls. So there should be an overall net gain. It applies the concept of 'First Time Right' from the manufacturing industry to the pharma. Despite the many financial and operational benefits of QbD, and even with the new FDA recommendations, not all companies have adopted this approach. As the saying goes "you either pay now, or pay later." Implementing QbD beginning at the development phase requires a dedicated, disciplined, and sustained commitment by the organization. Understanding the effort necessary to implement QbD is a key component to successful adoption. Some of the most common barriers to adoption include:

- Insufficient understanding of the process and its benefits
- Organizational resistance to change
- Denial of the need ("Our process is under control")
- Competing priorities.
- Lack of resources and expertise in QbD.[22]

When we consider the tremendous potential for financial gain, faster time to market, process improvements, and quality assurance generated by a successful implementation of QbD, these obstacles seem to smooth in assessment. Since QbD is successfully adopted in pharmaceutical industry, there are some problematic challenges noticed. Key challenges are evaluated by their relevancy against different drug types as well as different levels of adoption are as follows:

- The first four challenges occur within companies
  - Internal misalignment (i.e., Disconnect between cross functional areas, e.g., R&D and manufacturing or quality and regulatory)
  - Lack of belief in business case (e.g., "There is a lot of uncertainty over timing of and investment requirements for QbD implementation")
  - Lack of technology to execute (e.g., Difficulty Managing data, limited understanding of Critical Quality Attribute (CQA) implications)
  - Alignment with third parties (i.e., How to implement QbD with increasing reliance on suppliers and contract manufacturers?)
- The next six challenges are directly related to the FDA
  - Inconsistency of treatment of QbD across FDA (e.g., "Although a number of people in the FDA are supportive of QbD — this is not consistent")
  - Lack of tangible guidance for industry (e.g., FDA says "We understand what you are asking for broadly, but there are hundreds

of variables — there's got to be an end in mind — a tangible one we can deliver on")
- Regulators not prepared to handle QbD applications (i.e., reviewers at different levels of understanding and acceptance)
- Regulatory benefits are currently being shared does not inspire confidence (e.g., "At the end of the day it's still unclear whether FDA will actually back these filings")
- Misalignment of international regulatory bodies (i.e., Difficulty gaining acceptance of QbD applications in other countries)
- Current interaction with companies is not conducive to QbD (e.g. FDA says "we are treated with suspicion, it does not feel like collaboration.")

Levels of adoption of QbD among companies

Companies are at very different places in terms of adoption of QbD. Some companies are still skeptical (doubting) about the ideas of QbD and have not made much change towards a QbD approach. While others have fully implemented the concept and they are designing every product in development along a QbD framework. Most are in between these extremes.

Where companies fall on this arena will play a large role in how the FDA should interact with them.

- *Novice:* Company is skeptical about the value QbD can bring. Utilizes conventional development and has no platform.
- *Pilot:* Company is trying QbD, but still on the fence about the potential value. Tends to apply QbD to a small subset of projects and processes and has implemented limited or no plat forming.
- *Rollout:* Company is convinced about impact of QbD and is beginning to see some of the benefits. Uses QbD techniques regularly, but not universally. May engage in some lifecycle management with integrated platform and network strategy.
- *Fully implemented:* Company is completely convinced about the positive impact of QbD and is realizing the benefits. Uses QbD in almost every development program and almost every production step. Additionally, has a systematic, comprehensive review and re-design of in-line products.

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