Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2010, 2(2): 111-130
(http://scholarsresearchlibrary.com/archive.html)

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Quality by design: A systematic approach to pharmaceutical development

Mayank Nagar[1], Kamal Singh Panwar[1], V. S. Chopra*[1], Indu Bala[2], Piyush Trivedi[2]

[1]*Ranbaxy Laboratories Limited, Dewas, M.P., INDIA*
[2]*School of Pharmaceutical Sciences, R.G.P.V Bhopal, M.P., INDIA*

Abstract

The use of QbD principles during product development provides opportunities to facilitate innovation and continual improvement throughout the product lifecycle, compared to traditional approaches hence it is systematic way to product and process development. QbD principles increase process knowledge and product understanding, often through the application of new technologies such as PAT or modeling. The increased process knowledge and product understanding resulting from QbD can increase the efficiency of manufacturing processes; reduce product recalls and compliance actions, resulting in cost savings for pharmaceutical companies. By reducing uncertainty and risk, QbD can allow industry and regulators to focus their resources in the most critical areas. Because much more process understanding has been demonstrated and expressed in the dossier, QbD filings also can help facilitate CMC reviews and GMP inspections by the regulators and decrease the number of post-approval regulatory submissions required to make process changes. 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.

Key Words:-quality by design (QbD), continual improvement, process analytical technique (PAT), chemical manufacturing and control (CMC), good manufacturing properties (GMP), validation.

INTRODUCTION

In practice, the ideal QbD-based pharmaceutical development effort will involve a systematic method relating mechanistic understanding of input material attributes and process parameters to drug product critical quality attributes. Such a development effort is accomplished through the use of multivariate experiments involving modern process controls enabling process understanding. The QbD-based pharmaceutical manufacturing process will be adjustable within

a design space, providing a robust process that is managed with a control strategy developed using modern statistical process control methods and enabling a lifecycle approach to validation/continuous process verification. PAT tools with feedforward and feedback capabilities will facilitate continuous improvement efforts and provide the possibility of real-time release. Product specifications will be based on desired product performance characteristics and will be part of a risk-based quality control strategy.

The ICH Q8 (R1) draft guidance provides examples of possible approaches to achieving enhanced understanding of pharmaceutical products and processes. The International Society for Pharmaceutical Engineering (ISPE) launched the Product Quality Lifecycle Implementation (PQLI) initiative in June 2007 in US and a follow-up workshop was held in Europe in September. The intention of PQLI is to work with industry and regulatory agencies worldwide to facilitate a common understanding of Quality-by-Design (QbD), and introduce pragmatic and practical means for the implementation of ICH guidance's, based on sound scientific, engineering and business principles. The emphasis will initially be on providing 'how to' implementation guidance on ICH Q8, Q8 (R), Q9 and Q10 [1].

Pharmaceutical QbD is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control. Recently, the International Conference on Harmonization (ICH) has defined QbD in ICH Q8R as "a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management." It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. QbD identifies 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 can adapt and produce a consistent product over time [2].

A QbD development process may include (Fig. 1):

a. Begin with a target product profile that describes the use, safety and efficacy of the product
b. Define a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development
c. Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use risk assessment to prioritize knowledge gaps for further investigation
d. Design a formulation and identify the critical material (quality) attributes of the final product that must be controlled to meet the target product quality profile
e. Design a manufacturing process to produce a final product having these critical materials attributes.

f. Identify the critical process parameters and input (raw) material attributes that must be controlled to achieve these critical material attributes of the final product. Use risk assessment to prioritize process parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a design space or other representation of process understanding.
g. Establish a control strategy for the entire process that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment.
h. Continually monitor and update the process to assure consistent quality

Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools that may be used in the QbD process when appropriate. They are not check-box requirements [3].

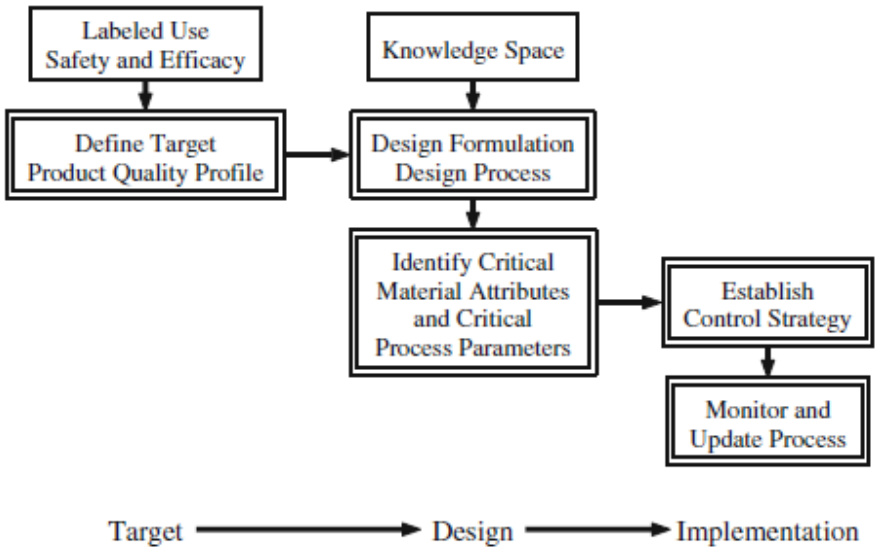

Figure.1. An overview of QbD process

Background of quality by design

The concept of quality by design is outlined in ICH Q8 (pharmaceutical development) that mention the definition of QBD that "QBD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management". The revision of ICH Q8, or ICH Q8 (R1), is an annex to ICH Q8. It provides further clarification of key concepts outlined in the core guideline and describes the principles of QBD.

Some elements of QbD have been used for many years. For example, the use of statistically designed experiments (DOE) dates back to the 1920's as factorial designs were applied in agricultural science, and the 1950's when they were more widely used for industrial applications. 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 spotlight on these techniques has intensified in the pharmaceutical industry, in particular with the United States Food and Drug Administration's (FDA) issuance of their report "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach". This report launched a strategic change towards the presentation of more scientific knowledge in submissions, thereby laying the groundwork for QbD. Shortly afterwards, FDA issued the guidance document, "PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance". Although the focus was more geared towards process analytical technology (PAT), this guidance document discussed many principles of QbD. Subsequent papers followed, such as the EMEA PAT. In 2005, ICH Q8 was issued which focused on the content of Section 3.2.P.2 of the Common Technical Document (CTD) and introduced the concept of design space2. An important step in defining the design space involves the differentiation between those product attributes and process parameters that are critical from those that are not. One common approach to achieve such decisions is the use of risk assessment. ICH Q9 was issued, which discusses potential approaches and tools that could be used to perform risk assessments, as well as the management of identified risks. The final document of the tripartite is ICH Q10, which addresses the quality management systems of pharmaceutical manufacturers. This guidance outlines expectations for the Pharmaceutical Quality System (PQS) 3, and how they can be applied in the management of the design space, risk assessment, and to ensure quality standards are met over the lifecycle of the product. ICH Q8(R), currently at Step 2, describes the principles of QbD and provides further clarification of key concepts outlined in ICH Q8. This annex is intended to show how concepts and tools could be put into practice by the applicant for all dosage forms. At the time of writing, both ICH Q10 and Q8 (R) are still subject to revision [4].

QBD involves the following key elements during pharmaceutical development:-

1. Define target product quality profile
2. Design and develop product and manufacturing processes
3. Identify critical quality attributes, process parameters, and sources of variability
4. Control manufacturing processes to produce consistent quality over time

1.Quality Target Product Profile (QTPP)

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

1. Effective optimization of a drug candidate
2. Decision-making within an organization
3. Design of clinical research strategies, and
4. Constructive communication with regulatory authorities.
5.

The TPQP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. For example, a typical QTPP of an immediate release solid oral dosage form would include:

– Tablet Characteristics
– Identity
– Assay and Uniformity
– Purity/Impurity
– Stability, and
– Dissolution

2.Design Product and Manufacturing Process

A. Product design and development

In order to design and develop a robust generic product that has the desirable TPQP, a product development scientist must give serious consideration to the biopharmaceutical properties of the drug substance. These biopharmaceutical properties include physical, chemical, and biological properties. Physical properties include physical description (particle size, shape, and distribution), polymorphism, aqueous solubility as function of pH, hygroscopicity, and melting points. Pharmaceutical solid polymorphism, for example, has received much attention recently. Its impact on product quality and performance has been discussed in recent review articles. Chemical properties include pKa, chemical stability in solid state and in solution as well as photolytic and oxidative stability while biological properties include partition coefficient, membrane permeability, and/or oral bioavailability. Biopharmaceutical properties should be assessed for every form for which there is an interest in development and every form that can potentially be created during processing (e.g., hydrates, anhydrates) or in vivo (e.g., less soluble salts, polymorphic forms, hydrates). The investigation of these properties is termed preformulation in pharmaceutical science.

The goal of preformulation studies is to determine the appropriate salt and polymorphic form of drug substance evaluate and understand its critical properties, and generate a thorough understanding of the material's stability under various processing and in vivo conditions, leading to an optimal drug delivery system. Pharmaceutical preformulation studies need to be conducted routinely to appropriately align dosage form components and processing with drug substance and performance criteria. Mechanical properties, though not often studied in detail, can have a profound impact on solid dosage form development and processing.

A sound understanding of mechanical properties of the drug and excipients can be useful in developing a processing method such as granulation or direct compression, rationally selecting excipients whose properties can compensate for the properties of the drug substance, and helping assess critical material attributes and root cause analysis during process scale-up or failure. Pharmaceutical materials can be elastic, plastic, viscoelastic, hard, soft, tough, or brittle. There exist various methods in the literature to evaluate these mechanical properties. The knowledge of mechanical properties of the drug and excipients are expected to play a more significant role in product design and development in the future. Drug-excipient compatibility has been identified as one of the most frustrating, troubling, and perplexing formulation challenges. Despite the fact that excipients can alter stability and bioavailability of drugs, the general principles of selecting suitable excipients for dosage forms are not well defined, and excipients are often selected without systematic drug-excipient compatibility testing. To avoid costly material wastage and time delays, ICH Q8 recommends drug-excipient compatibility studies to gain early prediction of drug-excipient compatibility. Systematic drug-excipient

compatibility studies offer several advantages: minimizing unexpected stability problems which usually lead to increases in time and cost; maximizing the stability of a formulation; and enhancing understanding of drug-excipient interactions that can help with root cause analysis if stability problems occur. Despite its significance, however, there is no universally accepted way to conduct drug-excipient compatibility studies in this evolving area. One method is thermal analysis, where a physical property of a substance (e.g., melting point) and/or reaction products is measured as a function of temperature while the substance is subject to a controlled temperature program. Another method utilizes isothermal stress. This method typically involves storing the drug-excipient blends or compacts with or without moisture at elevated temperature and determining drug content or degradation product formation as a function of time. Both methods can be used together to evaluate the compatibility of drugs with the selected excipients.

b. Process design and development

Process design is the initial stage of process development where an outline of the commercial manufacturing processes is identified on paper, including the intended scales of manufacturing. This should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables. Other factors to consider for process design are the target product quality profiles. Depending upon the product being developed, type of process, and process knowledge the development scientists have, it may be necessary to conduct preliminary feasibility studies before completing the process design and development. The selection of type of process depends upon the product design and the properties of the materials. For example, tablet manufacturing typically involves one of two methods: direct compression or granulation. Direct compression is the most straightforward, easiest to control, and least expensive tablet manufacturing process. It uses two primary unit operations, mixing and compression, to produce the finished tablet. Direct compression is used when ingredients can be blended, positioned onto a tablet press, and made into a high quality tablet without any of the ingredients having to be changed. When powders are very fine, fluffy, will not stay blended, or will not compress, then they may be granulated. Granulation is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. The dry granulation process is used to form granules without using a liquid solution. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be conducted on a tablet press using slugging tooling, or more typically on a roller compactor. Pharmaceutical development scientists have just begun making use of computer-aided process design (CAPD) and process simulation to support process development and optimization of manufacturing. Process simulation has been successfully used in the chemical and oil industries since the early 1960s to expedite development and optimize the design and operation of integrated processes. Similar benefits can be expected from the application of CAPD and simulation in the pharmaceutical industries. Currently, CAPD and process simulation are largely used in drug substance manufacturing. The utility of CAPD and process simulation in drug product design is limited. This is largely because the pharmaceutical industry has traditionally put emphasis on new drug discovery and development, and the complexity of drug product manufacturing operations are not well recognized. With the emphasis of QbD by the FDA and industry and drug product cost pressures, this trend is expected to change. The use of CAPD and process simulation should

result in more robust processes developed faster and at a lower cost, resulting in higher quality products.

3.Identify Critical Quality Attributes, Process Parameters and Sources of Variability

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 property or characteristic of an input or output material is defined as an attribute. Process parameters include the type of equipment and equipment settings, batch size, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture. The quality and quantity of drug substance and excipients are considered as attributes of raw materials. During process development, raw materials, process parameters and quality attributes are investigated. The purpose of these studies is to determine the critical raw material attributes, process parameters and quality attributes for each process, and to establish any possible relationships among them. Critical quality attributes (CQA) are physical, chemical, biological, or microbiological property or characteristic that must be controlled directly or indirectly to ensure the quality of the product. Critical process parameters (CPP) are process inputs that have a direct and significant influence on critical quality attributes when they are varied within regular operation range. Figure 2 Defines the CQA and CPP of wet granulation prior to process development.

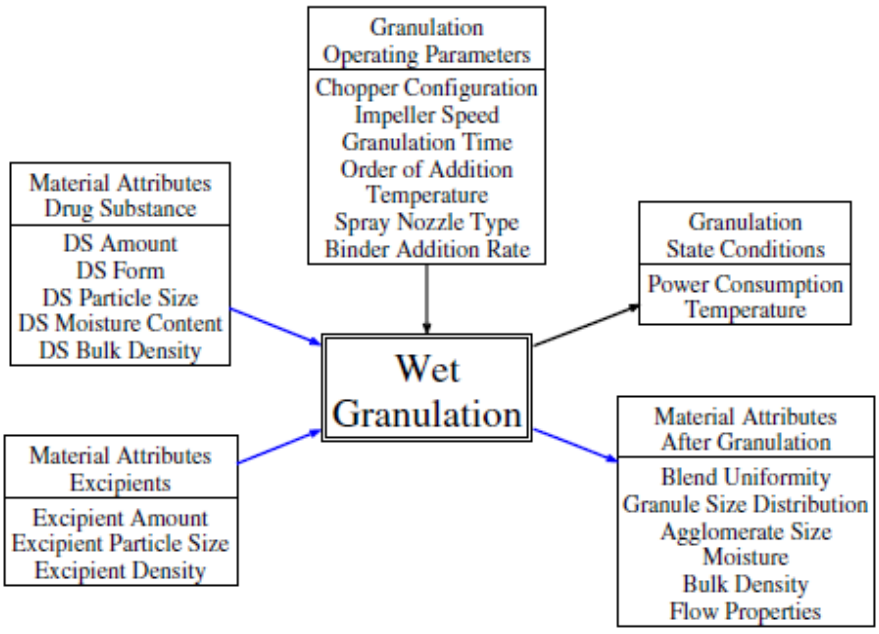

Figure 2 An example of identification of Process Parameters and Material Attributes Prior to Pharmaceutical Development

Criticality determines what quality attributes and process parameters are defined in the Design Space. The Design Space defines the relationship between Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs), and identifies acceptable operating ranges for CPPs. It is the region where acceptable product can be produced. The normal operating range is a subset of

the Design Space where routine manufacture is typically performed on a daily basis. Finally, the Control Strategy ensures that operation of the process is maintained within the Design Space. It is intended to prevent operating in regions of limited process knowledge or that are known to cause product failure. Figure 3 shows how these three elements are connected and interact with each other. The Knowledge Space is a summary of all process knowledge obtained during product development. It includes information about critical and non-critical attributes and process parameters. This encompasses the Design Space and normal operating ranges, as well as areas where it is known that unacceptable product is produced. The Knowledge Space only contains information regarding regions that have been investigated, and beyond its boundaries is considered to be unexplored space.

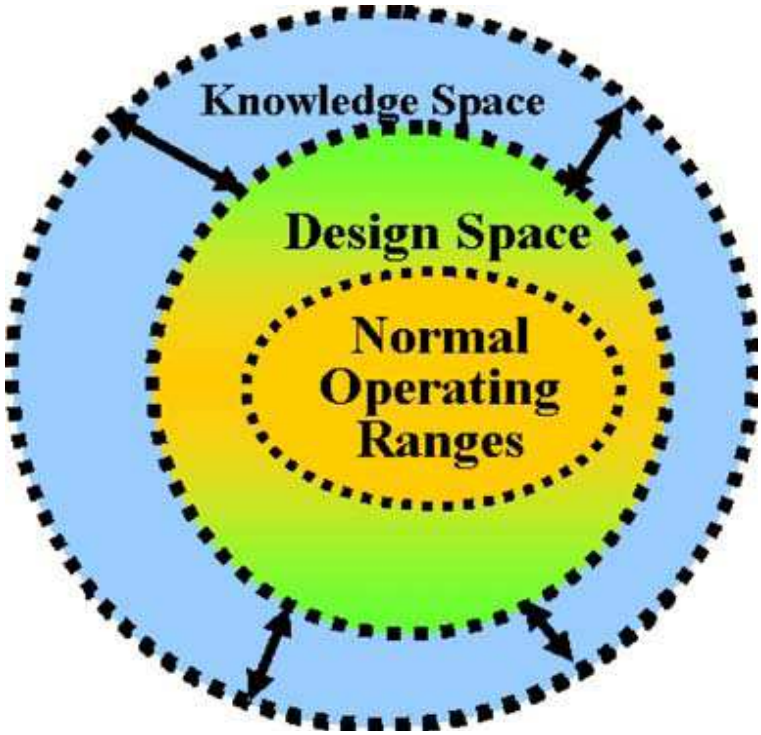

Figure3. Linkage between knowledge space, design space, and normal operating ranges
Criticality

The concept of criticality can be used to describe any feature or material attribute, property or characteristic of a drug substance, component, raw material, drug product or device, or any process attribute, parameter, condition or factor in the manufacture of a drug product. The assignment of attributes or parameters as critical or non-critical is an important outcome of the development process that provides the foundation for deciding what is or isn't included in the Design Space.

The Criticality Task Team concluded that establishing criticality is a process, rather than a simple definition. Underlying the process is the concept that the primary assessment and designation of criticality should be made relative to the impact that quality attributes or process parameters have on the safety, efficacy and quality of the product. In addition, the team looked for consistency with current accepted definitions and alignment with ICH guidance. The process

applies a series of filtering questions to determine if an attribute or process parameter impacts the safety, efficacy, or quality of the product. It relies on QbD. elements including risk assessment, the establishment of a Design Space, and the development of a Control Strategy. As the questions are answered, an attribute or parameter is taken down a specific path that categorizes its degree of criticality. With increased process knowledge and understanding, quality attributes and process parameters can undergo multiple iterations to reclassify their categorization, as necessary. Risk assessments should consider cause and effect relationships, relative to probability, severity, delectability, and sensitivity. Probability is the likelihood of harm occurring, while severity is the measure of the possible consequence. Detectability refers to the ability to discover or determine the existence, presence, or fact of a hazard, and sensitivity is the attenuation of interactions between multivariate dimensions. Using descriptive adjectives to define criticality with regard to these four elements clarifies the context associated with the risk.
Several levels of criticality may be used to describe multiple levels of risk. As the boundaries for a quality attribute or parameter approach edges of failure, the level of criticality increases with the level of risk. Following the risk assessment, some companies may choose to introduce additional optional terms such as 'key' or 'important'. Figure 4 therefore includes an additional category ("X") between the critical and non-critical classifications, to reflect this option. The purpose of this intermediate category is to address those attributes or parameters that may impact the safety, efficacy or quality of the product, but to a lesser degree than what is observed for other CQAs or CPPs. Attributes and process parameters in this intermediate category still warrants some attention, and their importance should not be overlooked; which could occur if they were categorized as being non-critical. Figure 5 define the decision tree to define the levels of criticality. Note that a Control Strategy or test does not make a CQA or CPP non-critical; but rather makes it controlled. As additional process information is obtained over the lifecycle of the product, it is possible that the criticality of some attributes or parameters may change. In such instances, changes in designation from one level of criticality to another must be demonstrated by data. If the change requires a change to the Control Strategy, then some measure of notification to regulatory authorities is required. Changes that do not result in a change to the Control Strategy may not require such notification.

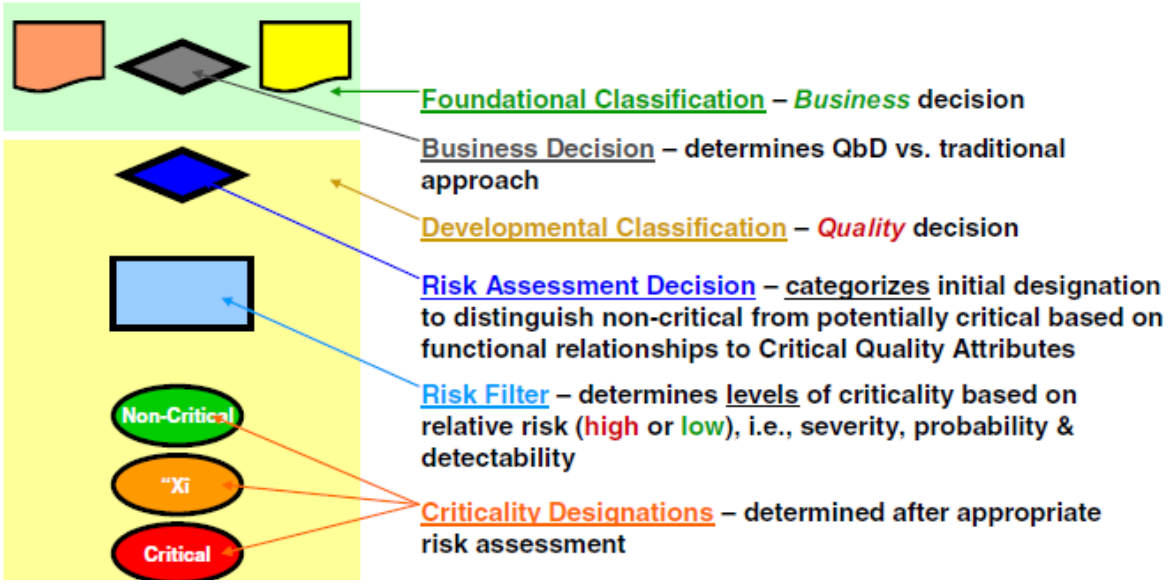

Figure4. Classification of criticality

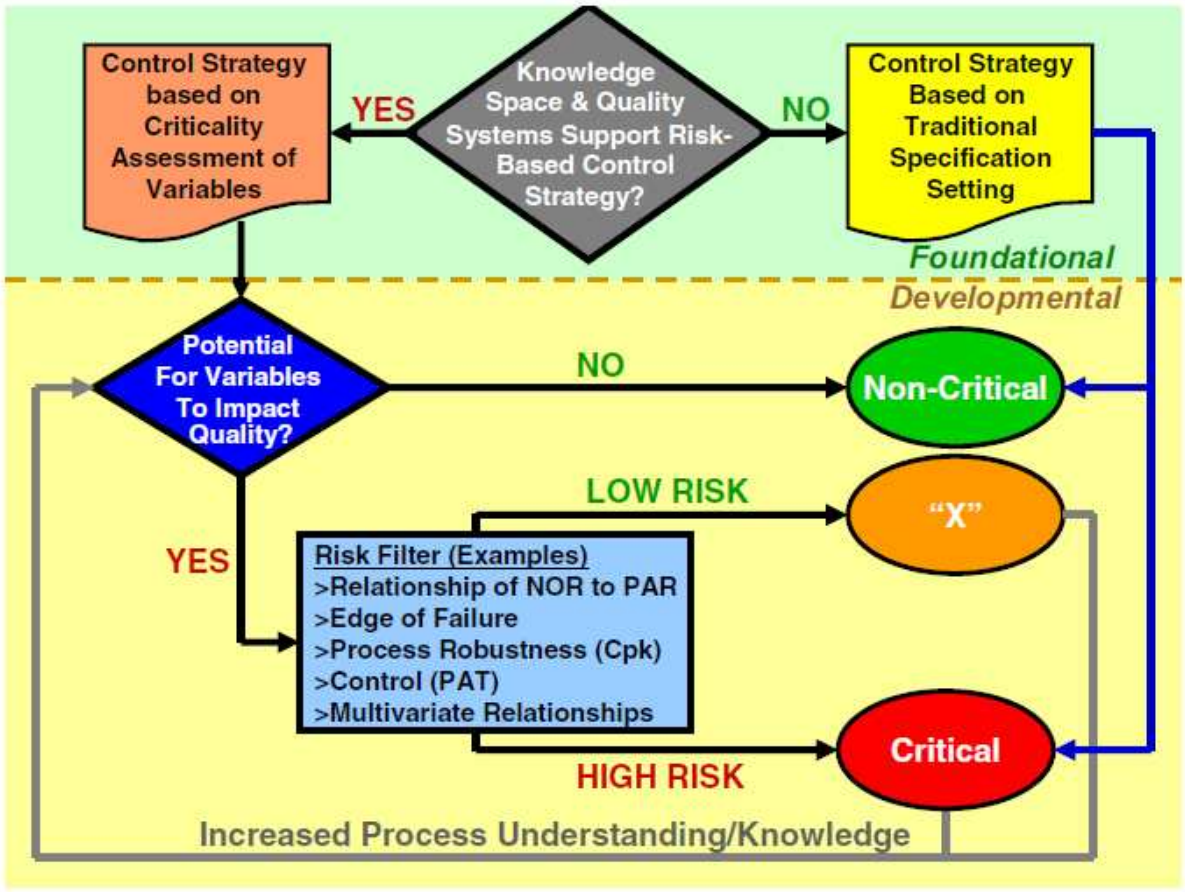

Figure5. Decision tree to define levels of criticality

Design space

The development and refinement of the Design Space begins at product conceptualization and continues to evolve throughout the lifecycle of the product. At the time of filing a submission, the Design Space can be considered to be a snap-shot in time representative of the current process knowledge. It continues to evolve as additional knowledge and information is generated during the commercialization of the product, which may lead to post-approval changes. Movement out of the Design Space is considered to be a change and would normally initiate a regulatory post approval change process. As such, the Design Space will require management under a company's Pharmaceutical Quality System. The creation of a Design Space begins with the definition of the Pharmaceutical Target Product Profile (PTPP), which identifies the desired performance characteristics of the product. Prior knowledge and a preliminary risk assessment can be used to identify experiments to be performed for the initial investigation into the importance of quality attributes and process parameters. The quality of raw materials (including API, solvents, starting materials, excipients, and packaging components) should be assessed, and any critical quality attributes identified. As development continues, additional risk assessments can occur that define subsequent experiments that lead to an understanding of the interactions between different attributes and process parameters. In addition, multivariate models based on chemistry, biotechnology, or engineering fundamentals can be used to build the Design Space. These models can be based on first principles, be empirical in nature, or a combination of both.

The intent of the experimentation and modeling is to create an understanding of all variables that impact CQAs, and represent the linkage in the form of a Design Space. This representation includes key links to risk assessment, the Control Strategy, and the Pharmaceutical Quality System.

The Design Space is linked to criticality through the results of risk assessment, which determines the associated CQAs and CPPs. It describes the multivariate functional relationships between CQAs and the CPPs that impact them, and should include their linkage to or across unit operations. Such relationships are arrived at by iterative application of risk assessment and experimental design, modeling, as well as the use of literature and prior experience. 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 Pharmaceutical Quality System. The Design Space may also contain operating ranges for process parameters classified in the intermediate criticality category discussed previously. 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.

Methods for determining design space included: one-variable-at-a-time experiments, statistically designed experiments, and modeling approaches. Methods for presenting design space included graphs (surface-response curves and contour plots), linear combination of parameter ranges, equations, and models [5].

Example1: Response graphs for dissolution are depicted as a surface plot (Figure 6a) and a contour plot (Figure 6b). Parameters 1 and 2 are factors of a granulation operation that affect the dissolution rate of a tablet (e.g., excipient attribute, water amount, granule size.)

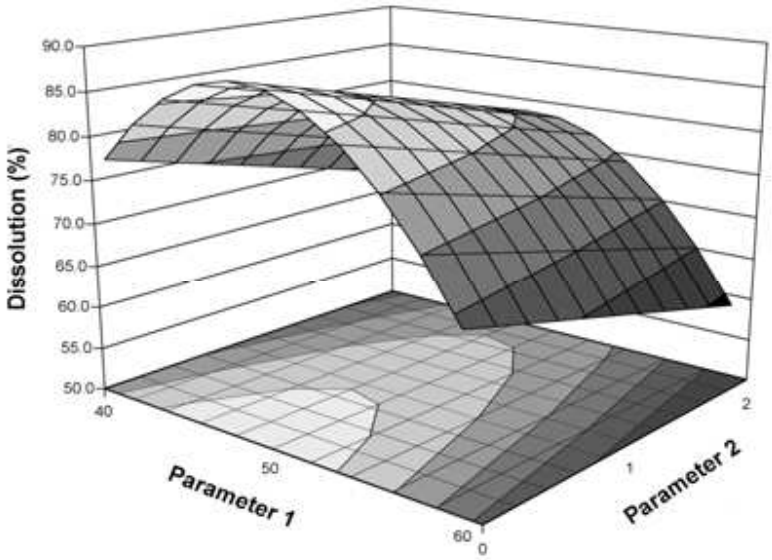

Figure 6a: Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired

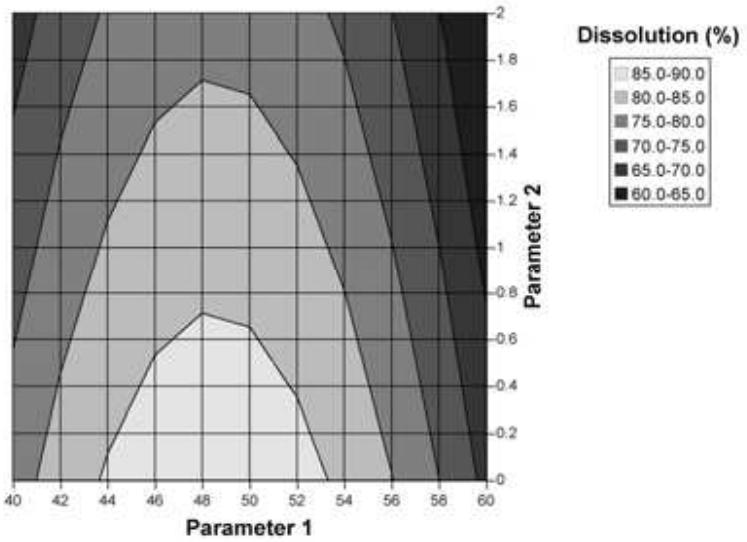

Figure 6b: Contour plot of dissolution from example 8a

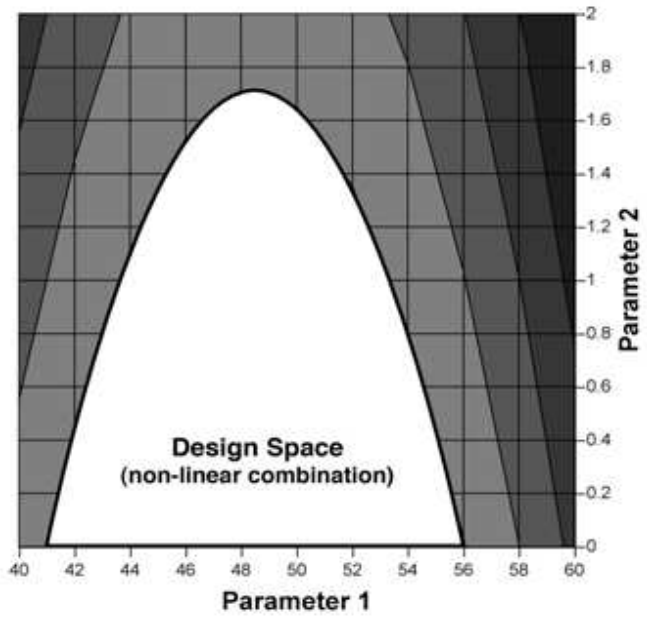

Figure 6c: Design space for granulation parameters, defined by a nonlinear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%)

In Figure 6c, the design space is defined by a nonlinear combination of parameter ranges that delivers the dissolution critical quality attribute. In this example, the design space is expressed by the response surface equation resolved at the limit for satisfactory response (i.e., 80% dissolution). The acceptable range of one parameter is dependent on the value of the other. For example:

If Parameter 1 has a value of 46, then Parameter 2 has a range of 0 and 1.5
If Parameter 2 has a value of 0.8, then Parameter 1 has a range of 43 and 54

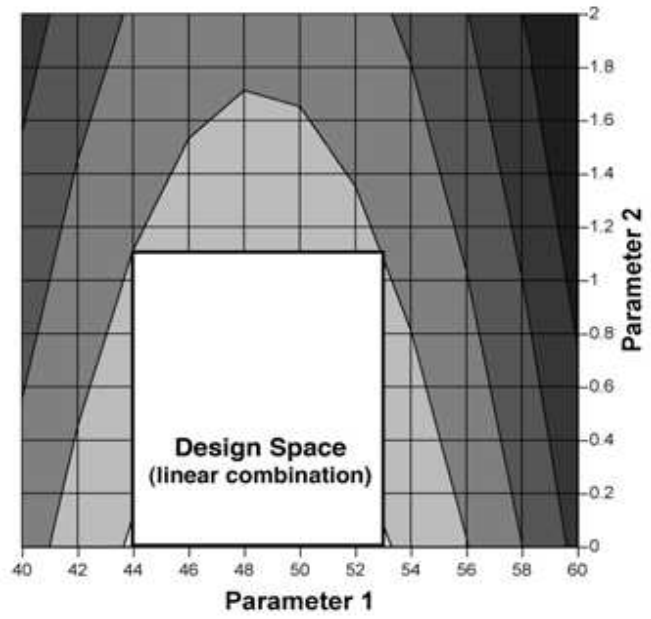

Figure 6d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%)

The approach in Figure 6c allows the maximum range of operation to achieve the desired dissolution rate. In Figure 6d, the design space is defined as a smaller range, based on a linear combination of parameters.

Parameter 1 has a range of 44 and 53
Parameter 2 has a range of 0 and 1.1

This example discusses only two parameters and thus can readily be presented graphically. When multiple parameters are involved, the design space can be presented for two parameters, in a manner similar to the examples shown above, at different values (e.g., high, middle, low) within the range of the third parameter, the fourth parameter, and so on. Alternatively, the design space can be explained mathematically through equations describing relationships between parameters for successful operation.

Source of variability

A comprehensive pharmaceutical development approach will generate process and product understanding and identify sources of variability. Sources of variability that can have an impact on product quality should be identified, appropriately understood, and subsequently controlled. Understanding sources of variability and their impact on downstream processes or processing, in-process materials, and drug product quality can provide an opportunity to shift controls upstream and minimize the need for end-product testing. Product and process understanding, in combination with quality risk management (see ICH Q9), will support the control of the process such that the variability (e.g., of raw materials) can be compensated for in an adaptable manner to deliver consistent product quality.

This process understanding can enable an alternative manufacturing paradigm where the variability of input materials could be less tightly constrained. Instead, it can be possible to design an adaptive process step (a step that is responsive to the input materials) with appropriate process control to ensure consistent product quality.

When the process is under the stage of continuous improvements there is less chance of process variability, means there is no drift and sudden change in the process. This process is called in the stage of statistical control. When the process is in stage of statistical control there is no need of the process control. By study the interaction of the process variables and quality attributes in design space (figure7) the process variability can be reduced and the process will be in the stage of statistical control.

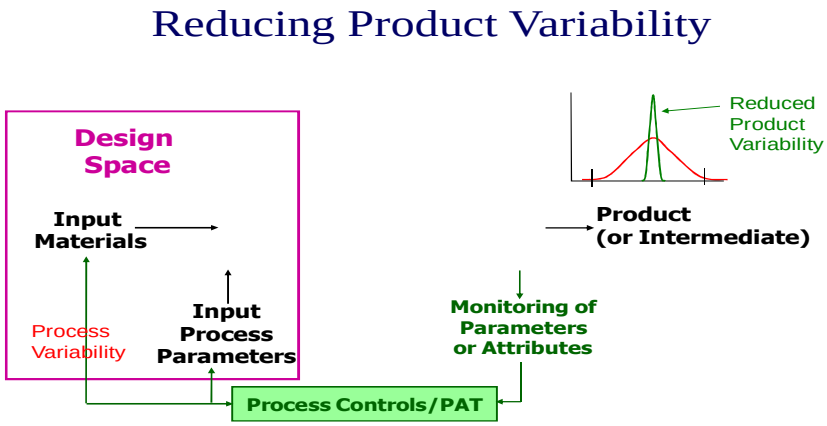

Figure7. Reducing product variability by process control

4.Control manufacturing processes to produce consistent quality over time

Control strategy

ICH Q10 defines a control strategy as "a planned set of controls derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications and the associated methods and frequency of monitoring and control."

Control Strategy is not a new concept - products have always had a more or less explicit control strategy - but in ICH Q8(R) (Step 2) document a 'Minimal Approach' to Control Strategy is contrasted with the 'Enhanced, Quality by Design Approach'. In the latter, the control strategy is closely linked to both criticality and the Design Space. The results of the risk assessment identify those CQAs and CPPs that are included in the Design Space and subsequently must be included in the Control Strategy. The Control Strategy may include, for example, raw material purchase specifications, API characteristics, operating ranges for process parameters, in-process controls and their corresponding acceptance criteria, release testing, and API or drug product specifications and their acceptance criteria. The ISPE PQLI Control Strategy Task Team has proposed a model that is intended primarily as a tool for pharmaceutical companies to facilitate communication and understanding of the concept and provide a framework for a structured

approach to the development and implementation of a Control Strategy, particularly using the 'enhanced approach' described in ICH Q8R. Assume that a model contains three levels showing links from the finished product CQAs and other objectives through the manufacturing operations to the controls by which these are achieved. Two columns distinguish between patient and business requirements. At Level 1 the Critical Quality Attributes (CQAs) and other requirements are identified. Level 2 considers the critical process parameters, material attributes and components involved in meeting the CQA requirements. Level 3 covers the actual analytical, automation, and other controls of the Level 2 identified parameters and attributes.

Thus the FDA CMC reviewers must act conservatively. A QbD based control strategy is shown in Fig. 8. Pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables to assure the quality of the finished product. The end product testing only confirms the quality of the product. In this example, PAT provides tools for realizing the real time release of the finished product although its use is not required under the paradigm of the Quality by Design.

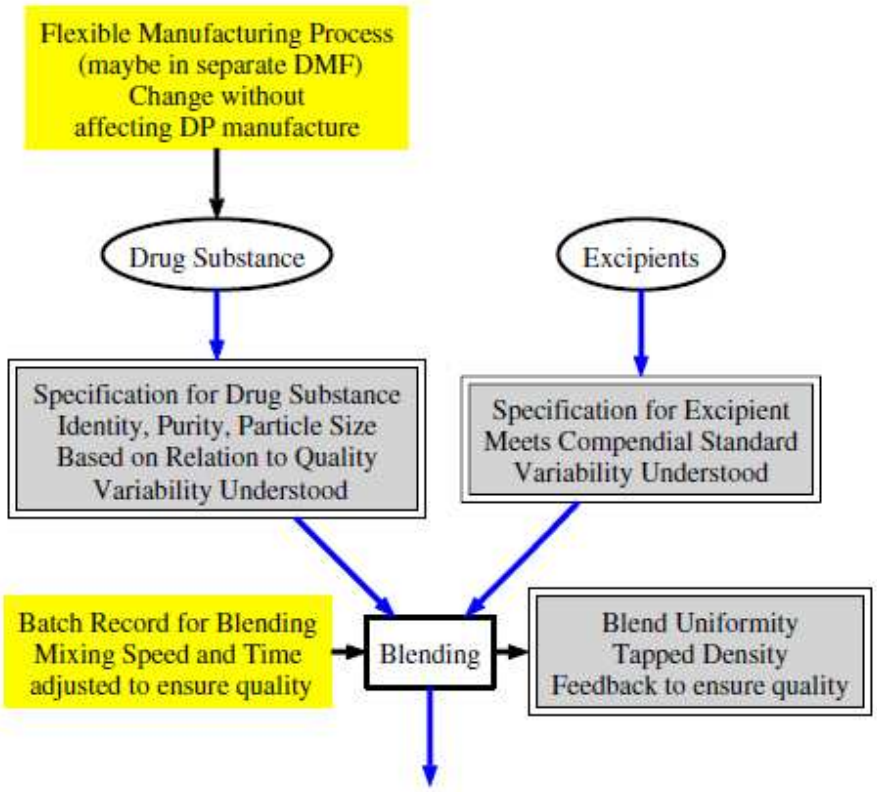

Figure8. Example of control strategy for QbD process

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.

Process capability is denot**ed by Cp**, it is the measured, inherent variation of the product turned out by the product. The most widely accepted formula for process capability is six sigma.

Process capability (Cp) = +-3standard deviation (total of 6 sigma)

Standard deviation= it is the S.D. of the process that is under the statistical control means under no drift and sudden change.

Cp refers the variation in a process about the average value, but average of process is not often the midpoint so it is useful to have the process capability index that reflects the both variation of process and the location of the process variation. **Process capability index** is the value of the tolerance specified for a particular characteristic divided by the process capability, which is defined as follows:

Process capability index (CpK) =

$$\frac{\text{Upper limit of specification - lower limit of specification}}{\text{6 standard deviation}}$$

If the CpK value is significantly greater than one, the process is deemed capable [6].

Maintain consistent quality over time

Product life cycle (figure9) starts with the process design and development and with the continuous improvements of the product. Under the first stage study the biopharmaceutical properties of the drug and raw materials. These biopharmaceutical properties include physical, chemical, and biological properties. Physical properties include physical description (particle size, shape, and distribution), polymorphism, aqueous solubility as function of pH, Hygroscopicity, and melting points. Pharmaceutical solid polymorphism, for example, has received much attention recently. Chemical properties include pKa, chemical stability in solid state and in solution as well as photolytic and oxidative stability while biological properties include partition coefficient, membrane permeability, and/or oral bioavailability.

Next step of the Product life cycle is the process design and development and process design is the initial stage of process development where an outline of the commercial manufacturing processes is identified on paper, including the intended scales of manufacturing. This should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables. Other factors to consider for process design are the target product quality profiles.

The third step is manufacturing development in which manufacturing process is designed for product. 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. In manufacturing process design the process parameters and product attributes are considered.

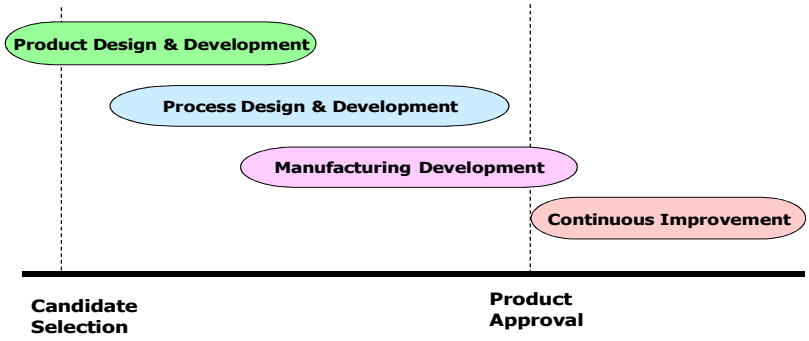

Figure 9. Product development and lifecycle

The fourth step of product life cycle is continuous improvements. Process performance can be monitored to ensure that it is working as anticipated to deliver product quality attributes as predicted by the design space. This monitoring could include trend analysis of the manufacturing process as additional experience is gained during routine manufacture. For certain design spaces using mathematical models, periodic maintenance could be useful to ensure the model's performance. The model maintenance is an example of activity that can be managed within a company's own internal quality system provided the design space is unchanged. Figure14 shows the continuous improvements for quality system.

Why use quality by design concept?

Pharmaceutical quality by testing is a current approach in the pharmaceutical system, 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. The quality of raw materials including drug substance and excipients is monitored by 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. Because of uncertainty as to whether the drug substance specification alone is sufficient to ensure quality, the drug substance manufacturing process is also tightly controlled. A change to the drug substance manufacturing process may require the drug product manufacturer to file supplements with the FDA. Finished drug products are tested for quality by assessing whether they meet the manufacturer's proposed and FDA approved specifications. If not, they are discarded. Root causes for failure are usually not well understood. The manufacturers risk ongoing losses of the product until the root causes of failure are understood and addressed or FDA approves supplements to revise (e.g., widen) the acceptance criteria to pass the previously failed batches. Typical specifications for an immediate release oral solid dosage form, for example, include assay, uniformity, impurities, moisture, and dissolution. Under the current paradigm, the specification is tight because it is used to assure consistency of manufacturing processes. The stringent specification has resulted in recalls and drug shortages but pharmaceutical QbD is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and

process control. QbD allows the real time release of the product because it has no scope of product failure with respect to quality. Under the QbD, batches may not be actually tested against the specification as the process understanding and/or process control provides sufficient evidences that the batches will meet the specification if tested, which allows the real time release of the batches. Further, the specification under the QbD is solely used for the confirmation of product quality, not manufacturing consistency and process control.

Under the QbD paradigm, pharmaceutical quality for generic drugs is assured by understanding and controlling formulation and manufacturing variables. End product testing confirms the quality of the product and is not part of the manufacturing consistency or process control. Under QbT a product specification is often set by observing data from a small number of batches believed to be acceptable and then setting acceptance criteria that required future batches to be the same.

Under QbD consistency comes from the design and control of the manufacturing process and the specification of drug product under QbD should be clinically relevant and generally determined by product performance.

The specifications for assay and dissolution often evaluate the most important characteristics drug tablets must have to ensure their effectiveness. It is interesting to note that the assay limit is currently determined in a manner that is closer to the QbD approach than to the QbT approach. The assay limit is normally set to be 90–110% with the exception a few selected drugs where there are clinical reasons for narrower acceptance limits, for example, 95–105%. Assay limits are not routinely set by using batch data.

Table1. Comparison of QbT and QbD approach

S. No.	QbT approach	QbD approach
1.	Quality assured by testing and inspection	Quality built into product & process by design, based on scientific understanding
2.	Data intensive submission – disjointed information without “big picture”	Knowledge rich submission – showing product knowledge & process understanding
3.	Specifications based on batch history	Specifications based on product performance requirements
4.	“Frozen process,” discouraging changes	Flexible process within design space, allowing continuous improvement
5.	Focus on reproducibility – often avoiding or ignoring variation	Focus on robustness – understanding and controlling variation

A sponsor that routinely produced drug product with an assay of 98– 100% would still expect an assay limit of 90–110%. However current dissolution acceptance limits of tablets are selected based on data from a small number of batches in the context of their ability to distinguish batches with limited regard to clinical relevance. Under the QbD, the dissolution tests should be developed to reflect in vivo performance as much as possible. For example, the acceptance criteria for BCS Class I and III IR tablets may be much wider than that from batch data because,

for these BCS classes, dissolution is highly unlikely to be the rate limiting step in vivo. Similarly, dissolution tests for BCS Class II and IV drugs may need to be carefully examined to better reflect in vivo dissolution. The specification for impurities assesses another important characteristic a drug product must have to ensure its safety. Table (1) shows the comparison of current QbT approach and pharmaceutical QbD approach.

CONCLUSION

Quality by design is an essential part of the modern approach to pharmaceutical quality. This paper clarifies the use of QbD for pharmaceutical development including:

a. Emphasis on the importance of the Target Product Quality Profile in articulating a quantitative performance target for QbD. Identification of critical material attributes that provide a mechanistic link of the product quality to the manufacturing process.
b. Clarification that critical process parameters are operating parameters and should be combined with critical material attributes to describe the relation between unit operation inputs and outputs.
c. The role of the control strategy as the mechanism for incremental implementation of QbD elements into practice
d. An efficient path to a design space through the identification of non-interacting process variables and their exclusion from formal experimental designs.

Quality by design is an evolving process in the pharmaceutical industry. ICH gives guidelines for the QbD in the Q8 (R1) Anx. QbD provides real time release of the product and reduce the risk of failure hence cost of failure. Under the QbT, each batch has to be tested against the specification to ensure its quality and manufacturing consistency. Under the QbD, batches may not be actually tested against the specification as the process understanding and/or process control provides sufficient evidences that the batches will meet the specification if tested, which allows the real time release of the batches so QbD is a better approach than QbT. Interaction of the raw material and process parameter with CQAs is important part of the QbD. Design space is the multidimensional combination and interaction between process parameter and quality attributes of the product. If we change the process parameter within the design space then the product will be of predefined quality. When the process is running within design space then no need to control the process but if the process is running out of design then there is need of process control and process improvements so that the process will give the product with desired QTPP and predefined quality. Six sigma continuous improvement approach is used to control the process which have five phases: define, measure, analyze, improve and, control phase. Process capability is used to determine whether the process is capable or not. If the CpK value is greater than 1, then the process is capable. QbD is novel approach which is currently being used in pharmaceutical industry than empirical approaches of the product development because it reduces the product variability.

REFERANCES

[1] Drennen III JK. *J Pharma Innov* **2008**. 2:65-66
[2] Yu Lx. *Pharmaceutical Research*, vol.25,no.4, April **2008**;781-791

[3] Lionberger RA, Lee SA, Lee LM, Raw A, Yu LX. The *APPS Journal*, Vol 10. 2 June **2008**; 268- 276
[4] Gracia T, Cook G, Nosal R. PQLI. *J pharm Innov* **2007**. 2: 87- 92
[5] ICH Q8 (R1), 2008b. Pharmaceutical Development. Part I: Pharmaceutical Development,
a. And Part II: Annex to Pharmaceutical Development., http://www.ich.org/LOB/media/ MEDIA4986.pdf.
[6] Gryna FM, Chua RCH, Defeo JA. Juran's Quality Planning and Analysis For Enterprise. Edn 5, Tata MacGraw-Hill Publishing Company Ltd, New Delhi, **2007**, PP. 67-199, 689-694
[7] Portillo PM, Ierapetritou M, Tomassone S, Dade CM, Clancy D, Avontuur PPC, Muzzio FJ. *J Pharma Innov* **2008**; 3: 258-270
[8] Ende DA, Bronk KS, Mustakis J, Connor GO, Maria CLS, Nosal R, Watson TJN. *J Pharm Innov* **2007**. 2:71- 86
[9] Cogdill RP, Drennen JK. *J Pharm Pnnov* **2008**. 3:23-29
[10] Dicknson PA, Lee WW, Stott PW, Townsend AI, Smart JP, Ghahramani P, Hammett T, Billett L, Behn S, Gibb Rc, Abrahamsson B. *APPS Journal*, Vol 10, No 2, June **2008**. 280-290
[11] Arnurn PV. A FDA Perspective on Quality by Design.
[12] Aegis Analytical Corporation. Quality by Design is Essential in New Regulatory Environment, http://www.aegiscorp.com
[13] ICH Q9, **2005**. Quality Risk Management., http://www.ich.org/LOB/media/ MEDIA1957.pdf.
[14] Nesh RA, Wachter AH. Pharmaceutical Process Validation. Edn 3, Marcel DAKKER Inc, Newyork, **2005**. PP. 452-454
[15] Kourti K. Quality by Design in the Pharmaceutical Industry: The Role of Multivariate analysis.
[16] Gryna FM, Chua RCH, Defeo JA. Juran's Quality Planning and Analysis For Enterprise. Edn 5, Tata MacGraw-Hill Publishing Company Ltd, New Delhi, **2007**, PP. 67-199, 689-694
[17] ICH Q10, 2008a. Pharmaceutical Quality Systems., http://www.ich.org/LOB/ media/MEDIA3917.pdf.
[18] VonBehren D, Quality by Design: The Automated Pharmaceutical assay: An Overview. SOTAX Corporation. PP.1-5
[19] Huang J, Kaul G, Chatapalli R, Hernandez-Abad P, Ghosh K, Nagi A. *International Journal of Pharmaceutics*. **2009**;382:23-32
[20] Wu H, Tawakkul M, White M, Khan MA. *International Journal of Pharmaceutics*. **2009**; 372:39-48
[21] Chen C, Moore C. Role of Statistics in Pharmaceutical Development Using Quality-by-Design Approach- An FDA Perspective. In the Proceeding of FDA/ Industry Statistics Workshop. Sep 27-29, **2006**
[22] Winkle HN. Implementing Quality by Design. In the proceeding of PDA/FDA Joint Regulatory Conference: Evolution of the Global Regulatory Environment: A Practical Approach TO Change. Sep 24, **2007**
[23] Weinberg s, Fugua R. A stochastic Model of "Quality by Design" For the Pharmaceutical industry.
[24] Feiler S, Solot Ph. Quality by Deign of Experiments: How Can design Of Experiments Be Used in Efficient Development, as specified In the ICH Q8 and PAT Guidelines. AICOS Technologies Ag.