Research Article

Quality by Design: A Paradigm for Industry

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ABSTRACT

Quality by Design (QbD) refers to a holistic approach towards drug development. The quality in the process and product is neither assures just by inspection nor testing the products, the quality should be built in by design. QbD is the concept of continuous gaining of relevant knowledge based on scientific principles and the information gained from pharmaceutical development and manufacturing experiences which implement into designing quality product. Under this concept of QbD during designing and development of a product, a company needs to define desire product performance profile [Target Product Profile (TPP), Target Product Quality Profile (TPQP)] and identify Critical Quality Attributes (CQA). To achieve respective CQAs the Fish Bone Diagram is desired one and to check variations in process, the Six Sigma approach is very significantly used. The use and implementation of the attributes and models is in accordance to the ICH Q8, ICH Q9 & ICH Q10. The pharmaceutical industry works hard to develop, manufacture, and bring to market new drugs—and to comply with regulatory requirements to demonstrate that the drugs are safe and effective. A new approach to drug development could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product's life cycle. This article explores the processes used in developing a market formulation and requisite supportive data, particularly in light of the industry's current movement toward submissions based on quality by design (QbD).

Keywords: Critical Quality Attributes (CQA), Fish Bone Diagram, Quality by Design, Quality Profile (TPQP), Target Product Profile (TPP), Target Product Six Sigma Approach.

INTRODUCTION

History[1]

The pharmaceutical industry has been a highly regulated industry in the past for many good reasons. While pharmaceuticals have greatly improved the mortality and morbidity rates, there is still some element of risk to the patients. These risks are greatly mitigated with the delivery of medicine at the appropriate purity, potency, delivery rate, and so on. The twenty-first century began with the pharmaceutical industry using manufacturing technologies that have been employed since the 1940s and did not make significant changes in manufacturing process unless significant compliance or costs saving advantages could justify the high costs and long cycle time needed to gain approval. Finally, the current Good Manufacturing Practices (cGMPs) for the Twenty-First Century Guidance acknowledged the undesired impact of good manufacturing practices (GMPs) on understanding manufacturing science and sought to set the framework for additional guidance that encouraged risk and science-based understanding in exchange for more freedom to introduce innovations and improvements that will result in enhanced quality, cost, or timing. Juran is often credited with introducing the concepts behind Quality by Design (QbD). Pharmaceutical QbD is a systematic approach to development that begins with pre-defined objectives and emphasizes product and process understanding based on sound science and quality risk management (ICHQ8R2). The holistic and systematic approach of QbD was relatively new to the pharmaceutical industry at the beginning of the twenty-first century.

Quality[2]

Quality has become one of the most important consumer decision factors in the selection among competing products and services. ICH Q8 defines quality as "the suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity. Quality means fitness for use. Quality is inversely proportional to variability."

Dimensions of Quality

Performance (Will the product do the intended job?)

Reliability (How often does the product fail?)

Durability (How long does the product last?)

Serviceability (How easy is it to repair the product?)

Aesthetics (What does the product look like?)

Features (What does the product do?)

Perceived Quality (What is the reputation of the company or its product?)

Conformance to Standards (Is the product made exactly as the designer intended?)

Definitions of Quality[3, 4]

1) Manufacturing based definitions

- Quality means conformance to requirements.
- Quality is a degree to which a specific product confirms to a design or specifications.

2) User based definitions

- Quality consists of the capacity to satisfy wants.
- Quality is degree to which a specific product satisfies the wants of the specific consumer.
- Quality is fitness for use.

3) Product Based Definitions

- Difference in quality amounts to differences in the quantity of some desired ingredient or attribute.
- Quality refers to the amount of unprized attributes to contain in each unit of the priced attributes.

4) Transcended Definitions:

- Quality is neither mind nor matter, but a third entity independent of the two, even though cannot be defined you know what it is.

The Food and Drug Administration (FDA) Office of Generic Drugs (OGD) has developed a question-based review (QbR) for its chemistry, manufacturing, and controls (CMC) evaluation of abbreviated new drug applications (ANDAs). This new QbR system incorporates some elements of QbD. The main benefits of this QbR system are to assure product quality through design and performance-based specifications. The concept of QbD was mentioned in the ICH Q8 guidance, which states that **"quality cannot be tested into products i.e. quality should be built in by design".** The pharmaceutical industry works hard to develop, manufacture, and bring to market new drugs and to comply with regulatory requirements to demonstrate that the drugs are safe and effective.

QUALITY BY DESIGN (QbD)[5, 6]

This concept was first outlined by well-known quality expert Joseph M. Juran on Quality by Design. In the late 1990 FDA"s internal discussion began and in the year 2002 the concept paper on 21st century Good Manufacturing Practice was published. Quality by design (QbD) encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications. Quality by Design (QbD) refers to a holistic approach towards drug development. QbD has become the answer to assist both industry and FDA to move towards a more scientific, risk based, holistic and proactive approach to pharmaceutical development. The concept promotes industry's understanding of the product and manufacturing process starting with product development, basically building quality in, not testing it. In addition to this new concept being considered by FDA in its cGMP initiative, two important guidance documents were published as part of International Conference on Harmonization (ICH) guidelines: Q8 Pharmaceutical Development and Q9 Quality Risk Management. The former describes the expectations for the pharmaceutical development section of the Common Technical Document (CTD); the later presents approaches to producing quality pharmaceutical products using current scientific and risk based approaches. Q10 Pharmaceutical Quality System also describes model for an effective quality management system for pharmaceutical industry. This paper describes progress made by the Design Space within the Product Quality Lifecycle. It is intended to provide approaches to the rational development of Design Space, as well as background on Design Space, its historical origins and how it fits within the wider initiative.

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Advantages of QbD[7, 8]

- It provides a higher level of assurance of drug product quality.
- It offers cost saving and efficiency for the pharmaceutical industry.
- It increases the transparency of the sponsor understands the control strategy for the drug product to obtain approval and ultimately commercialize.
- It makes the scale-up, validation and commercialization transparent, rational and predictable.
- It facilitates innovation for unmet medical needs.
- It increases efficiency of pharmaceutical manufacturing processes and reduces manufacturing costs and product rejects.
- It minimizes or eliminates potential compliance actions, costly penalties, and drug recalls.
- It offers opportunities for continual improvement.
- It provides more efficiency for regulatory oversight:
- It streamlines post approval manufacturing changes and regulatory processes.
- It more focused post approval cGMP inspections.
- It enhances opportunities for first cycle approval.
- It facilitates continuous improvement and reduces the CMC supplement.
- It enhances the quality of CMC and reduces the CMC review time.

PHARMACEUTICAL QUALITY BY TESTING (QbT)[8]

Traditionally, pharmaceutical quality was defined as the product meeting the pre-specified quality attributes and regulatory specification. There is no link between the product quality attributes and clinical performance. In quality by testing (QbT) raw materials, in process and finished products are monitored by testing. Fig.1 shows a simplified quality control diagram under the quality by testing (QbT) regulatory framework for generic drugs. 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. Finished products are tested for quality by assessing whether they meet the manufacturers proposed or FDA approved specifications. If not, they are discarded and generally root caused for failure are not understood. The stringent specification has resulted in recalls and drug shortage.

Simply QbT is an IPQC test that usually carried out at the time of production process. Such assurance of quality at the time of production is done by testing the disintegration, hardness, physical evaluation like colour, odour and weight variation.

Table 1: QbD over QbT[5]

QbT Approach	QbD Approach
Quality assured by testing and inspection	Quality built into product & process by design, based on scientific understanding
Data intensive submission – disjointed information without "big picture"	Knowledge rich submission – showing product knowledge & process understanding
Specifications based on batch history	Specifications based on product performance requirements
"Frozen process," discouraging changes	Flexible process within design space, allowing continuous improvement
Focus on reproducibility – often avoiding or ignoring variation	Focus on robustness – understanding and controlling variation

Quality by Design Steps for Implementation[12-14]

The Target Product Quality Profile (TPQP)

In order to design quality into a product, the requirements for the product design and performance must be well understood in the early design phase. In pharmaceuticals, these product requirements can be found in a Quality Target Product Profile (QTPP). The QTPP is derived from the desired labelling information for a new product. Pharmaceutical companies will use the desired labelling information to construct a target product profile that describes anticipated indications, contraindications, dosage form, dose, frequency, pharmacokinetics, and so on. The target product profile is then used to design the clinical trials, safety and ADME studies, as well as to design the drug product, that is, the QTPP.

Target Product Quality Profile (TPQP) is a tool for setting the strategic foundation for drug development — "planning with the end in mind." The target product profile (TPP) has been defined as a "prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized". Target Product Quality Profile (TPQP) is a term that is a natural extension of TPP for product quality. It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label.

Steps of QbD Implementation [10]

Figure 1: Steps of Qbd Implementation

TPQP is related to identity, assay, dosage form, purity, stability in the label 20, 21 For example, a typical TPQP of an immediate release solid oral dosage form would include 22

– Tablet Characteristics

– Identity

– Assay and Uniformity

– Purity/Impurity

– Stability, and

– Dissolution

The TPQP of a generic drug can be readily determined from the reference listed drugs (RLD). Along with other available information from the scientific literature and possibly the pharmacopeia, the TPQP can be used to define product specifications to some extent even before the product is developed. Predefined, high quality product specifications make the product and process design and development more objective and efficient.FDA

published a recent guidance defining a Target Product Profile (TPP): "The TPP provides a statement of the overall intent of the drug development program, and gives information about the drug at a particular time in development. A generic product may use a different formulation or design to implement the TPP. The characteristics and performance tests of a drug product would depended on the particular implementation and may differ between a generic and reference product. For a new drug, changes to the TPP may require new safety or efficacy data, but changes to product characteristics or performance that result from a reformulation may not. Many aspects of the TPP constrain or determine the actions of formulation and process development scientists.

Critical Quality Attributes (CQA)[14]

Once TPP has been identified, the next step is to identify the relevant CQAs. A CQA has been defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality". Establish a link between CPP & CQAs: Identification of attribute or parameters that can be used as a surrogate for clinical safety & efficacy. Identification of CQAs is done through risk assessment as per the ICH guidance Q9. Prior product knowledge, such as the accumulated laboratory, nonclinical and clinical experience with a specific product-quality attribute, is the key in making these risk assessments. Such knowledge may also include relevant data from similar molecules and data from literature references. This information provides a rationale for relating the CQA to product safety and efficacy. The use of robust risk assessment methods for identification of CQAs is novel to the QbD paradigm.

The use of CQA can be reserved for cases where there is a need to refer collectively to the targets of a QbD approach. CQA is generally assumed to be an attribute of the final product, but it is also possible to indicate a CQA of an intermediate or a raw material. Although many people have identified dissolution as a critical quality attribute, we consider that a set of critical material attributes (CMAs) that are independent of each other provide specific goals with which to evaluate a manufacturing process. For example a dissolution test may depend on particle size and hardness. Particle size and hardness are CMAs which can be directly linked to raw materials and manufacturing process parameters. Independent CMAs are the best way to provide a mechanistic link of the product quality to the critical process parameters in the manufacturing process.

Critical Process Parameter[16]

Critical Process Parameter (CPP) as any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency. We propose that process parameter be understood as referring to the input operating parameters (mixing speed, flow rate) and process state variables (temperature, pressure) of a process or unit operation. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials. Monitoring and controlling output material attributes can be a better control strategy than monitoring operating parameters especially for scale up. A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TPQP. Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider. A simple example is that an impeller speed of zero will always fail.

Table 2: Examples of CQAs & CPPs[15]

Unit operation	Critical Process Parameter	Critical Quality Attributes
Roll Compaction	Roll Speed, Gap Setting, Roll Pressure, Screen Size, Screen Type.	Particle Size, Ribbon Density Ribbon Strength Appearance
Compression	Pre-Compression Force, Main compression Force, Press Speed – Dwell Time, Force Feeder Speed, Feeder Type, Hopper design, Tablet weight and thickness, Depth of Fill, Punch Penetration Depth.	Target Weight Weight Variation Hardness and Variation Friability Content Uniformity Assay, Disintegration Dissolution, Tablet porosity
Coating	Product Temperature Total Pre heating Time Spray Nozzle (Type/ Pattern/ Configuration) Spray Rate (Total/ Individual), Pan Rotation Speed, Atomization Air pressure, Inlet air flow, temperature, dew point, Total Coating Time, Gun Location, Gin to bed distance.	Appearance Visual attributes % weight gain Film thickness Colour uniformity Hardness Thickness friability

Cause and Effect Diagram or Fish Bone Diagram[17, 18]

Fish bone diagram also called as Ishikawa Diagram. A Risk Assessment Tool is nothing but fish bone diagram. One of the new technique is used to identified the Critical Process Parameter is Cause and Effect diagram or we say Fish Bone Diagram. This type of diagram looks like a fish bone skeleton so that's why is called fish bone diagram. Whatever to achieve the CQAs of the target product profile there is a need to identify the CPP of the system. The following diagram gives the idea about the selection and following that attributes. The team could then rank the variables based on probability, severity, and detect

ability using failure mode effects analysis (FMEA) or similar tools based on prior knowledge and initial experimental data. Design of experiments or other experimental approaches could then be used to evaluate the impact of the higher ranked variables, to gain greater understanding ofthe process, and to develop a proper control strategy.

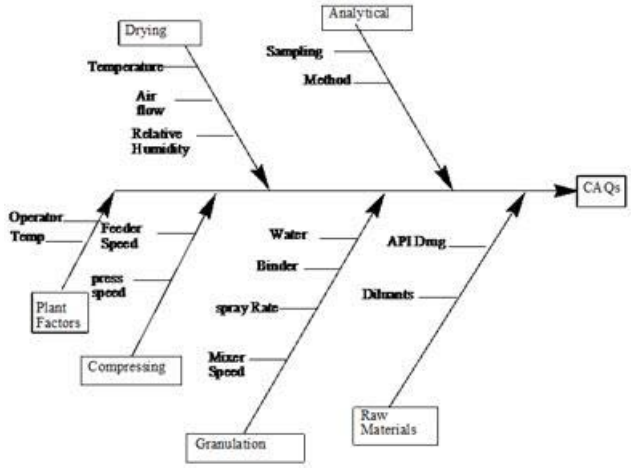

Figure 2: Fish Bone Diagram to Achieve CQAs

Design Product and Defining Product Design Space[16]

After CQAs for a product have been identified, the next step is to define the product design and design space (that is, specifications for in-process, drug substance and drug product attributes). These specifications are established based on several sources of information that link the attributes to the safety and efficacy of the product, including, but not limited to, the Published literature on other similar products, Process capability with respect to the variability observed in the manufactured lots, Design space, Clinical and nonclinical studies with similar platform products. ICH Q8 (R1) defines design space 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. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Because design space is potentially scale and equipment-dependent, the design space determined at the laboratory scale may not be relevant to the process at the commercial scale. Therefore, design-space verification at the commercial scale becomes essential unless it is demonstrated that the design space is scale-independent. Currently, generic-drug sponsors obtain information about acceptable ranges for individual CPPs and CMAs at laboratory or pilot scales. Sponsors may occasionally conduct these studies with appropriate design of experiments, including multivariate interactions, which will create a design space at the laboratory or pilot scale. In QbD, an improved understanding of the linkages between the CQA and safety and efficacy of the product is required. QbD has brought a realization of the importance of the analytical, nonclinical and animal studies in establishing these linkages and has led to the creation of novel approaches. 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.

Process Design and Defining Process Design Space[19]

Process and product design and development cannot be separated since formulation cannot become a product without a process. Process design is the initial stage of process development where an outline of commercial manufacturing processes is identified including the intended scale of manufacturing. The Design Space also contains the proven acceptable ranges (PAR) for CPPs and acceptable values for their associated CQAs. 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.

Process robustness is defined as the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time. 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 characteristics. 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,

$$\text{Process Capability Index} = \frac{\text{Upper limit of specification} - \text{lower limit of specification}}{\text{Standard Deviation}}$$

If the CpK is significantly greater than one, the process is defined capable. If the process capability is low, Rath and Strong recommend an iterative five step procedure to progressively reduce the variability of the process.

Six-Sigma Approach to check variations in designing the process[20]

Motorola developed the **Six-Sigma program** in the late 1980s. The focus of six-sigma is reducing variability in key product quality characteristics to the level at which failure or defects are extremely unlikely. The Motorola six-sigma concept is to reduce the variability in the process so that the specification limits are at least six standard deviations from the mean.

When the six-sigma concept was initially developed, an assumption was made that when the process reached the six-sigma quality level, the process mean was still subject

to disturbances that could cause it to shift by as much as 1.5 standard deviations off target.

Table 3: Variation in Cost of Quality By Six Sigma

Sigma	ppm Defect	Yield	Cost of Quality
2σ	308,537	69.2%	25-35%
3σ	66,807	93.3%	20-25%
4σ	6,210	99.4%	12-18%
5σ	233	99.98%	4-8%
6σ	3.4	99.99966%	1-3%

(6σ-world class, 5σ-superior, 4σ-healthy, 3σ-Average, 2σ-not capable, 1σ- not competitive.)

Defining Control Strategy[20]

Control strategy is defined as "a planned set of controls, derived from current product and process understanding that assures process performance and product quality". 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 is testing, process monitoring, characterization testing, comparability testing and stability testing. It is worth noting that the use of risk assessment in creating the control strategy is unique to the QbD approach.

Process Validation

An enhanced understanding of the manufacturing process and an expanded process design space should provide more manufacturing flexibility during process validation. Because the process designs space "assures quality" of the drug product, these limits should also provide the basis of the validation acceptance criteria. The limits that establish the acceptable variability in product-quality and process performance attributes would also serve as the process validation acceptance criteria. Once the process design space has been created, process validation becomes an exercise to demonstrate (i) that the process will deliver a product of acceptable quality if operated within the design space and (ii) that the small and/or pilot scale systems used to establish the design space accurately model the performance of the Manufacturing scale process. Thus, in the QbD paradigm, unanticipated manufacturing excursions that remain within the process design space should not jeopardize the success of the validation exercise.

Cost of Quality[22]

Financial controls are an important part of business management. Many organizations now formally evaluate the cost associated with quality. There are several reasons why the cost of quality should be explicitly considered in an organization. The reasons are like –

1. The increase in the cost of quality because of the increase in the complexity of manufactured products associated with advances in technology.
2. Increasing awareness of life-cycle costs, including maintenance, spare parts, and the cost of field failures.
3. Quality engineers and managers can most effectively communicate quality issues in a way that management understands.

Table 4: Types of Quality Cost

Prevention cost	Internal failure cost
Quality planning and engineering	Scrap
New products review	Rework
Product design	Retest
Process design	Failure analysis
Training	Downtime
Quality data acquisition and analysis	Yield losses

Appraisal cost	External failure cost
Inspection and test of incoming material	Complaint adjustment
Product inspection and test	Returned product/material
Materials and services consumed	Warranty charges
Maintaining accuracy of test equipment	Liability costs Indirect costs

Cost of Quality Models [CoQ]

Plunkett and Dale suggest that the most striking feature of their literature review is the preoccupation with the prevention-appraisal-failure (P-A-F) model.

Table 5: Models to Judge Cost of Quality

Generic models	Cost / activity categories
P-A-F Model	Prevention + appraisal + failure
Crosby's Model	Conformance + non-conformance
Opportunity or intangible cost models	Prevention + appraisal + failure + opportunity
	Conformance + non-conformance + opportunity
	P-A-F (failure cost includes opportunity cost)
Process cost Models	Conformance + non-conformance
ABC models	value-added + non-value-added

The objective of a CoQ system is to find the level of quality that minimizes total cost of quality. The basic suppositions of the P-A- F model are that investment in prevention and appraisal activities will reduce failure costs, and that further investment in prevention activities will reduce appraisal costs The cost categories of **Crosby's model** (Crosby, 1979) are similar to the P-A-F scheme. Crosby sees quality as "conformance to requirements", and therefore, defines the cost of quality as the sum of price of conformance and price of non-conformance.

Models in Quality by Design Paradigm[22-24]

Definition of model

A model is a representation of an underlying physical/chemical phenomenon.

Advantages of Models

- Enhanced Process Understanding.
- Reduction of Number of Experiment.
- Improvement of Productivity and Product Quality.
- Allows Decision Making.

QbD is the concept of continuous gaining of relevant knowledge based on scientific principles and the information gained from pharmaceutical development and manufacturing experiences which implement into designing quality product. There are various types of models that can be easily used in QbD paradigm. These models can be applied at any stage of the QbD; hence it is necessary to have knowledge of various models. The applications of the models are in accordance with the principles of ICH Q8, Q9 and Q10 guidelines.

ICH Q8 – Pharmaceutical Development

ICH Q9- Quality Risk Management

ICH Q10- Pharmaceutical Quality System

Thus, QbD requires an understanding how formulation and process variables influence product quality. The ICH Q8 guidelines specify minimum elements required during the pharmaceutical development.ICH Q9 guideline specify approaches to producing quality pharmaceutical products using current scientific and risk based approaches. Q10 Pharmaceutical Quality System also describes model for an effective quality management system for pharmaceutical industry.

Categorization of Models as Per Ich[28, 29]

The International Conference on Harmonization categorized the models used in QbD paradigm into three types depending on their level of impact on quality. These are as follows:

A) Low Impact Model: These models are typically used to support product and/or process development (e.g., formulation optimization).

B) Medium Impact Model: Such models can be useful in assuring quality of the product but are not the sole indicators of product quality (e.g., most design space models, many in-process controls.

C) High Impact Model: A model can be considered high-impact if prediction from the model is a significant indicator of quality of the product (e.g., a chemo metric model for product assay, a surrogate model for dissolution).

Types of Models [31]

Table 6: Types of Models[30, 31, 32]

Mechanistic model	Empirical model	Semi- Empirical / Hybrid Model
• Computational Fluid Dynamic (CFD) • Discrete Element Model (DEM) • Finite Element Model (FEM) • Thermodynamic model	• Chemo metric model • IV- IVC model • Neural Network model • Regression model	• Scale up Equation • Property Estimation

Examples of Models in QbD Paradigm[33]

1) Product Design

- Models to Optimize Formulations
- IV-IVC Models
- Reaction Kinetic Models

2) Process Design

- Scale up model to scale up parameter from pilot to Commercial scale
- Mechanistic models to Define design space
- Chemo metric models
- Multivariate models to support RTRT (surrogate models for dissolution)

3) Life cycle Management

- MSPC models for continual Experiment.

CONCLUSION

While QbD is most effective when it is employed at a product/process design level, it should also be accomplished in the manufacturing and quality assurance environments. Quality by design is a common understanding on the concepts of ICH Q8, Q9 and Q10 and will be essential in the process of formulation. The review explains the use of target product profile, risk assessment, identification the critical material attributes and clears the concept of critical process parameters, implements the control strategy and continues

monitoring and updating the process. It also explains application of QbD principles and tools to drug product and process development. The level of detail for describing a model in a regulatory submission is dependent on the impact of its implementation in assuring the quality of the product. Models can support pharmaceutical development as well as implementation of modern pharmaceutical manufacturing concepts e.g. design space, RTRT, continual process monitoring. To be successful QbD must facilitate a generic product development organization whose primary objective is to be first to file. Many R&D organizations within the generics industry are measured by the timing and number of ANDAs filed, not the quality of the ANDA.

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