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Pharmaceutical Quality by Design: A New Approach in Product Development.

Ashwini Gawade[1]*, Satyam Chemate[1], and Ashwin Kuchekar[2]

[1]P. Dr. V. V. P. F's. College of Pharmacy, Ahmednagar- 414001, Maharashtra, India.
[2]Bharti Vidyapeeth's Poona College of Pharmacy, Erandwane, Pune- 411038, Maharashtra, India.

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***Corresponding author**

P. Dr. V. V. P. F's. College of Pharmacy, Ahmednagar- 414001, Maharashtra, India.
Mobile: +91 9422088900

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ABSTRACT

Quality by Design (QbD) refers to a new approach to product development that could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product life cycle. It supports both industry and FDA to move towards a more scientific, risk based, holistic and proactive approach to pharmaceutical development. During designing and development of a product in QbD, a company needs to define desire product performance profile [Target Product Profile (TPP), Target Product Quality Profile (TPQP)] and identify critical quality attributed (CQA). The company then designs the product formulation and processes to meet the product attributes. This leads to understanding the impact of raw materials [Critical Material Attributes (CMA)], on the CQAs and identifies and control sources of variability. This systematic approach to product development and manufacturing has received a great deal from the traditional approach, which was extremely empirical. QbD is necessary in regulatory requirement, and to implement new concepts such as design space, International Conference on Harmonization's guidelines i.e. Q8 pharmaceutical development, Q9 quality risk management, and FDAs process analytical technology (PAT).

INTRODUCTION

A high quality drug product is a product free of contamination and reproducibly delivering the therapeutic benefit promised on the label to the consumer. 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."*A frequently used definition of quality is *"Delighting the customer by fully meeting their needs and expectations"*. These may include performance, appearance, availability, delivery, reliability, maintainability, cost effectiveness and price, and total customer satisfaction. It is important that quality should be built in by design. To achieve the high level of quality there is need of Quality by Design [1, 2].

Quality by Design

This concept was first outlined by well-known quality expert Joseph M. Juran on Quality by Design (J.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. With assistance of several biopharmaceutical companies, pilot programs were started to explore Quality by Design application and understandings [3, 4].

Definition

As per ICH Q8 (R2) Pharmaceutical Development 2009, QbD is defined as "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". 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

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that the drug product should possess, and establish how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics [2]. Table 1 explains the comparison of QbT approach to the desired QbD approach [5, 6].

Table 1: Comparison: QbT and QbD approach.

Elements	QbT approach	QbD approach
Product process development	Data intensive submission- disjointed information without 'big picture'	Knowledge rich submission- showing product knowledge and process understanding
	A specification based on batch history	A specification based on product performance requirements
	'Frozen process'-discouraging changes	Flexible process within the design space allowing continuous improvement
	Focus on reproducibility-often avoiding or ignoring variation	Focus on robustness-Understanding and controlling variations
Risk management	Compliance focus changes require prior approval	Regulatory scrutiny adjusted to the level of process understanding continuous improvement allowed within the design space
	Control strategy managed mainly by intermediate & end product testing	Risk based; control shifted up strong real-time release
	Quality decision divorced from science & risk evaluation	A decision based on process understanding & risk management
Validation	Fixed; validation on 3 initial full-scale batches, focus on reproducibility	Adjustable within the design space continuous verification within a design space; focus on control strategy & robustness
Process control	In-process testing for go/no-go offline analysis; slow response	Management of variability process control focused on critical attributes, continuous quality verification
	Quality assured by testing & inspection	Quality built into product & process by design, based on scientific understandings
Lifecycle management	Reacting to problems and OOS; post approval changes needed	Continual improvement enabled within the design space

Advantages of QbD [7]

- It provides a higher level of assurance of drug product quality.
- It offers cost savings 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.

Overview of Quality by Design Process

Quality by Design is a scientific risk based holistic and proactive approach to pharmaceutical development. It involves the designing and planning of a drug product and process before actual experiment. Over the past several years, pharmaceutical scientists have provided several more specific definitions of the elements of quality by design and a draft of an annexure to ICH Q8 has been released [2,8,9]. Overview of QbD process is explained in Figure 1.

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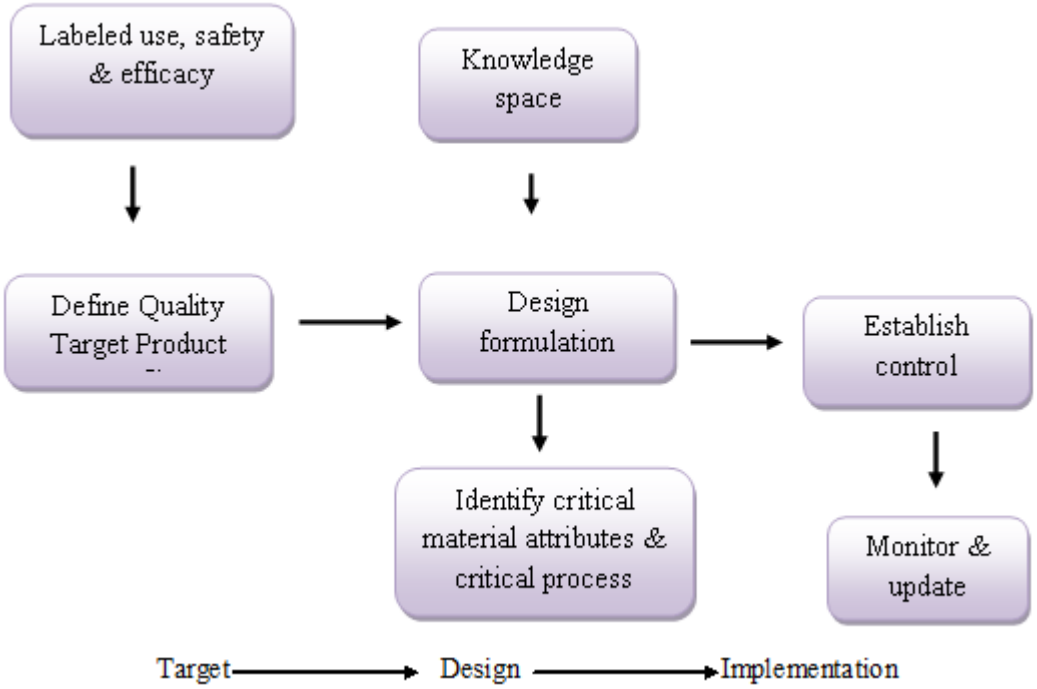

Figure 1: Overview of QbD process

Briefly a QbD development process includes stages as described below:

a. A target product profile describes the use, safety and efficacy of the product.
b. Defining a target product quality profile is used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development.
c. Drawing together relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use a risk assessment to prioritize knowledge gaps for further investigation.
d. Designing a formulation and identify the critical material attributes of the final product that must be controlled to meet the target product quality profile.
e. Designing a manufacturing process to produce a final product having critical material attributes.
f. Identifying the critical process parameters and raw material attributes that must be controlled to achieve critical material attributes of the final product. Use of 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. Establishing a control strategy for the entire process that may include input material controls, process controls. The control strategy should encompass expected changes in scale and can be guided by a risk assessment.
h. Continuous monitoring and updating the process to assure consistent quality.

Elements of quality by design [10]

a. Defining the target product quality profile

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 are realized". This includes dosage form and route of administration, dosage form strength(s), therapeutic moiety release or delivery and pharmacokinetics characteristics (e.g., dissolution and aerodynamic performance) appropriate to develop the drug dosage form and drug product-quality criteria for the intended marketed product as shown in Figure 2.

The 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. The TPQP guides formulation scientists to establish formulation strategies and keep formulation efforts focused and efficient. TPQP is related to identity, assay, dosage form, purity, stability in the label. Biopharmaceutical properties of drug substance include physical, chemical, and biological properties. A typical TPQP of an immediate release solid oral dosage form would includes:

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- Tablet Characteristics
- Identity
- Assay and Uniformity
- Purity/Impurity
- Stability, and
- Dissolution [11-14]

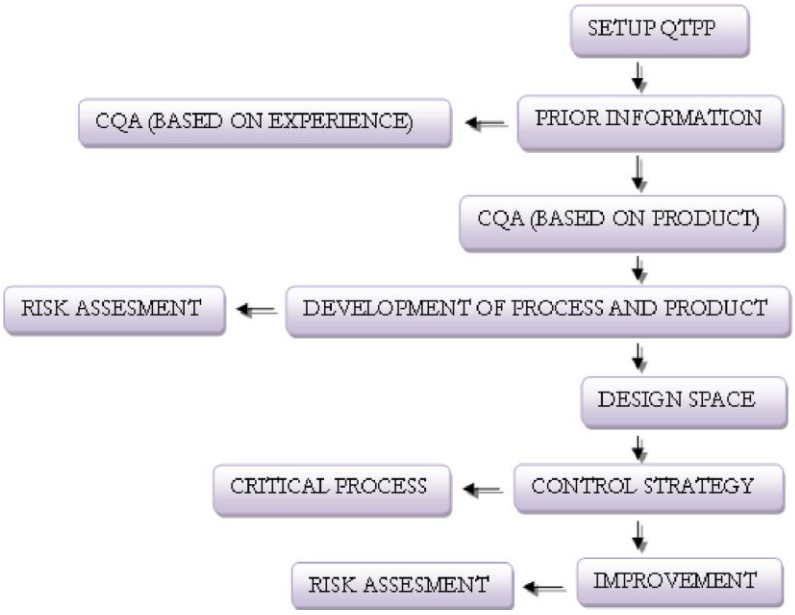

Figure 2: Elements of QbD

b. Identifying critical quality attributes

(For Drug substance, Excipients, Intermediates, Drug Product)

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 distributed to ensure the desired product quality" 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 [15].

c. Performing Risk Assessment

It is nothing but linking material attributes and process parameters to CQAs. ICH Q9 Quality Risk Management indicates that, the manufacturing and use of a drug product necessarily lead to some degree of risk. The evaluation of the risk of quality should be based on scientific knowledge and link to the therapeutic benefit to the patient. The level of effort, formality and documentation of the quality risk management process should be proportionate with the level of risk. Performing a risk assessment before pharmaceutical development helps manufacturers decide which studies to conduct. Study results determine which variables are critical and which are not, which then guide the establishment of control strategies for in-process, raw-material, and final testing.

Several applications in the CMC pilot included risk assessments, especially for the drug product by linking input and process variables to CQAs. Tools used in the risk assessment included the Ishikawa or Fishbone diagram, failure mode effect analysis (FMEA), 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 tablets hardness. An FMEA can be used to rank the variables based on risk (i.e., a combination of probability, severity, and detectability) and to select the process parameter with higher risks for further studies to gain greater understanding of their effects ion CQAs [16,17].

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d. Establishing Design Space

(Linkage between input variable and process parameter and CQAs)

ICH Q8 (R1) defines design space as, the multidimensional combination and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality. Moving 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 proposed by the applicant and is subject to regulatory assessment and approval. Design space is potentially scale and equipment dependent, the design space determined on 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 confirmed 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 [18, 19].

e. Defining Control Strategy

ICH Q8 (R1) defines control strategy as:

"A planned set of controls, derived from current product and process understanding that ensures 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.

Particularly, the control strategy may include:

- Control of raw material attributes (e.g., drug substance, excipients and primary packaging materials) based on an understanding of their impact on process-ability or product quality.
- Product specifications
- Procedural controls
- Facility controls such as utilities, environmental systems and operating conditions
- Controls for unit operations that have an impact on downstream processing or end-product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution)
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

The Control Strategy should establish the necessary controls based on patient requirements to be applied throughout the whole product life cycle from product and process design through to final product, including API and Drug Product manufacture, packaging and distribution [18, 20].

f. Life cycle Management and Continuous improvement

After approval, CQAs are monitored to ensure that the process is performing within the defined acceptable variability that served as the basis for the filed process design space. The primary benefit of an expanded process design space would be a more flexible approach by regulatory agencies. In the QbD paradigm, process changes within the design space will not require review or approval. Therefore, process improvements during the product life cycle with regard to process consistency and throughput could take place with fewer post approval submissions. In addition to regulatory flexibility, the enhanced understanding of the manufacturing process would allow more informed risk assessment as per ICH Q9 regarding the affects of process changes and manufacturing deviations on product quality. Manufacturing experience grows and opportunities for process improvement are identified, the operating space could be revised within the design space without the need for post-approval submission. Over the lifetime of a product, process changes may be required to be made and may require process characterization, validation and filing of the changes to the approved process design space. The quality system needs to provide adequate oversight during QbD implementation of changes that will not go through regulatory approval. Robustness of the quality system would need to be demonstrated with respect to the following four elements: process performance/product quality monitoring; preventative/corrective action, change management and management review of process performance and product quality [18, 21, 22].

Tools of Quality by Design

a. Design of Experiments (DOE)

Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. It has been suggested that DOE can offer returns that are four to eight times greater than the cost of running the

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experiments in a fraction of the time. A methodology for designing experiments was proposed by Ronald A. Fisher, in his innovative book *The Design of Experiments* (1935). Application of DOE in QbD helps in gaining maximum information from a minimum number of experiments. When DOE is applied to a 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 the 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 who do not, as well as details such as the existence of interactions and synergies between factors [2, 23] as in Figure 3, One Factor at a time and Design of experiments.

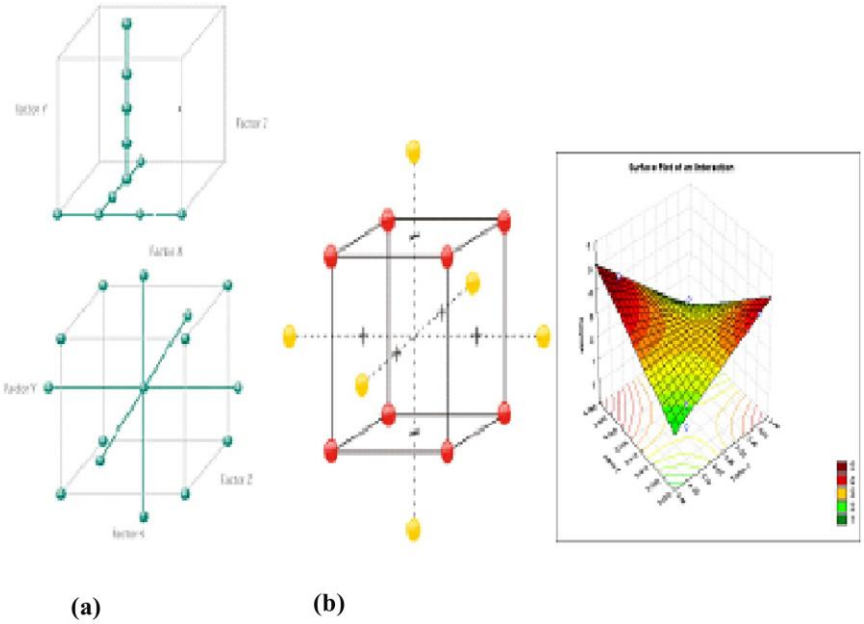

Figure 3: (a) One-factor-at-a-time method.(O-FAT) and (b) Design of experiment (DOE)

b. Process Analytical Technology (PAT)-

PAT has been defined as "A system for designing, analyzing, and controlling manufacturing through measurements, during processing of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality". The goal of PAT is to "enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design." The design space is defined by the key and critical process parameters identified from process characterization studies and their acceptable ranges. These parameters are the primary focus of on-, in- or at-line PAT applications. In principle, real-time PAT assessments could provide the basis for continuous feedback and result in improved process robustness. NIR act as a tool for PAT and useful in the RTRT (Real Time Release Testing) as it monitors the particle size, blend uniformity, granulation, content uniformity, polymorphism , dissolution and monitoring the process online, at the line and offline, thus it reduces the release testing of the product [24,25].

c. Risk Management Methodology

Quality Risk Management is defined as "A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle". Risk assessment is a helpful science-based method, used in the quality risk management that can help in identifying the material attributes and process parameters that potentially have an effect on product CQAs. Risk assessment is typically performed in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. In QbD, the management should be ensured and provided the risk- and science-based reviews, at critical milestones. For this purpose, the teams have to utilize risk assessment tools in the R&D lifecycle. One such critical milestone, prior to finalization of process technology, is a qualitative formulation. Decisions made at these milestones will generally impact the quality and costs attributes to a much greater extent than decisions made during process development and later in the product lifecycle.

Risk assessment tools can be used to identify and level parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and primary experimental data. The early list of potential parameters can be

fairly broad, but can be modified and prioritized by additional studies (e.g., through a combination of design of experiments, mechanistic models). The list can be developed further through experimentation to establish the significance of individual variables and potential interactions. Once the considerable parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding. The pharmaceutical industry and regulators can evaluate and manage risks by using well-known risk management tools and/ or internal procedures such as,

- Basic risk management facilitation methods (flowcharts, check sheets etc.);
- Failure Mode Effects Analysis (FMEA);
- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools [7, 22, 26].

Challenges of implementing QbD with FDA perspective

Implementation challenges include:

- Putting new concepts/ approaches into practice (QbD, Design space, Quality risk management)
- Diversity of products.
- Different regulatory processes (NDA, ANDA.BLA)
- Expectation for QbD-based submission while addressing traditional requirement's (dual process) Integration of review and inspection work in progress, Broad spectrum of approaches to development manufacturing, and quality operations across industry implementing, harmonizing Heavy workload and limited resources.
- Implementation challenges to industry includes culture change, information on application, Role of an industry scientist's in regulatory discussions, Business challenges includes removing silos across business units, remove budgeting silos across business units additional investment during development to achieve efficiency and lower manufacturing cost over Lifecycle, Management Support.
- Unpredictability of treatment of QbD across FDA [4, 27].

CONCLUSION

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. It can be concluded Quality by Design (QbD) principles and tools, play an important role in facilitating a higher level of process understanding and create opportunities for investigation and developing control strategies in formulation and process development.

Abbreviations-

ICH- International Conference on Harmonization
QbD- Quality by Design
FDA- Food and Drug Administration
QbT- Quality by testing
cGMP-current Good Manufacturing Practice
CMC-Chemistry Manufacturing and Control
TPP-Target Product Profile
CQA-Critical Quality Attributes
CPP-critical Process Parameter
DOE-Design of Experiments
PAT-Process Analytical Technology
NIR-Near Infra Rays
R&D-Research And Development

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