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QUALITY BY DESIGN: A NEW CONCEPT IN PHARMACEUTICAL PRODUCT DEVELOPMENT.

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ABSTRACT

Quality by Design (QbD) refers to a new approach in product development that could increase efficiencies, provide regulatory relief and flexibility 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.

KEYWORDS: Quality by design, Quality target product profile, Critical quality attributes, Design of experiment, Pharmaceutical manufacturing, Quality risk management, Design space.

INTRODUCTION

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. i.e. Total customer satisfaction. Quality starts with market research to establish the true requirements for the product or service and the true needs of the customers. So, at this stage the focus of quality is on the end product. 2 However, for an organisation to be really effective, quality must span all functions, all people, all departments and all activities and be a common language for improvement. 3.

What is next for 21st Century

QbD?

What is Quality by Design (QbD)? Quality by Design (QbD) is a concept first outlined by well-known quality expert **Joseph M. Juran** in various publications, most notably Juran on Quality by Design. Juran believed that quality could be planned, and that most quality crises and problems relate to the way in which quality was planned in the first place. While Quality by Design principles have been used to advance product and process quality in every industry and particularly the automotive industry, they have most recently been adopted by the U.S. Food and Drug Administration (FDA) as a vehicle for the transformation of how drugs are discovered, developed and commercially manufactured. This FDA imperative is best outlined in its report "Pharmaceutical Quality for the 21st Century: A Risk-Based Approach. In the past few years, the Agency has made significant progress in implementing the concepts of "Quality by Design" (QbD) into its pre-market processes. The focus of this concept is that quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks. This is a successor to the "quality by QC" (or "quality after design") approach that the companies have taken up until 1990s.

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 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.

Table 1: explains the comparison of QbT approach to the desired QbD approach

Aspect	Minimal approaches	Enhanced, QbD approaches
Overall pharmaceutical development	• Mainly empirical • Developmental research often conducted one variable at a time	Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs Multivariate experiments to understand product and process Establishment of design space PAT tools utilised
Manufacturing process	Fixed Validation primarily based on initial full-scale batches Focus on optimisation and reproducibility	Adjustable within design space. Lifecycle approach to validation & ideally. Continuous process verification. Focus on control strategy and robustness Use of statistical process control methods
Process control	In-process tests primarily for go/no go decisions Off-line analysis.	PAT tools utilised with appropriate feed forward and feedback controls. Process operations tracked and trended to support continual improvement efforts post approval
Product specification	Primary means of control. Based on batch data available at time of registration.	Part of the overall quality control strategy. Based on desired product performance with relevant supportive data
Control strategy	Drug product quality controlled primarily by intermediates (in process materials) and end product testing.	Drug product quality ensured by risk-based control strategy for well understood product and process. Quality controls shifted upstream, with the possibility of real-time release testing or reduced end-product testing
Lifecycle management	Reactive (i.e., problem solving and corrective action)	Preventive action. Continual improvement facilitated

ADVANTAGES OF QBD

Benefits for Industry

- Better understanding of the process.
- Less batch failure.
- More efficient and effective control of change.
- Return on investment / cost savings.

Additional opportunities

- An enhance QbD approach to pharmaceutical development provides opportunities for more flexible regulatory approaches.

Ex: Manufacturing changes within the approved design space without further regulatory review.

- Reduction of post-approval submissions.
- Better innovation due to the ability to improve processes without resubmission to the FDA when remaining in the Design Space.
- More efficient technology transfer to manufacturing.
- Greater regulator confidence of robust products.
- Risk-based approach and identification.
- Innovative process validation approaches.
- Less intense regulatory oversight and less post-approval submissions.
- For the consumer, greater drug consistency.
- More drug availability and less recall.
- Improved yields, lower cost, less investigations, reduced testing, etc.
- Continuous improvement over the total product life cycle (i.e. controlled, patient guided variability).
- Real time controls (less batch controls).
- Contributes substantially to realize the better, cheaper and safer mandate.

7-Step QbD Process for Pharmaceutical Product Development

- Quality target product profile
- Identify approach to drug product formulation/manufacturing process.
- Identify potential Critical Quality Attributes of RM/DS/DP
- Identify potential Critical Process Parameters
- Using risk assessment & experimental approaches, determine the functional relationships that link raw material CQAs and unit operation CPPs to drug product CQAs
- Refine formulation and manufacturing process, if necessary and repeat steps 3 -5 to meet QTPP defined in Step 1.
- Establish Design Space and Control Strategy.

ELEMENTS OF QUALITY BY DESIGN

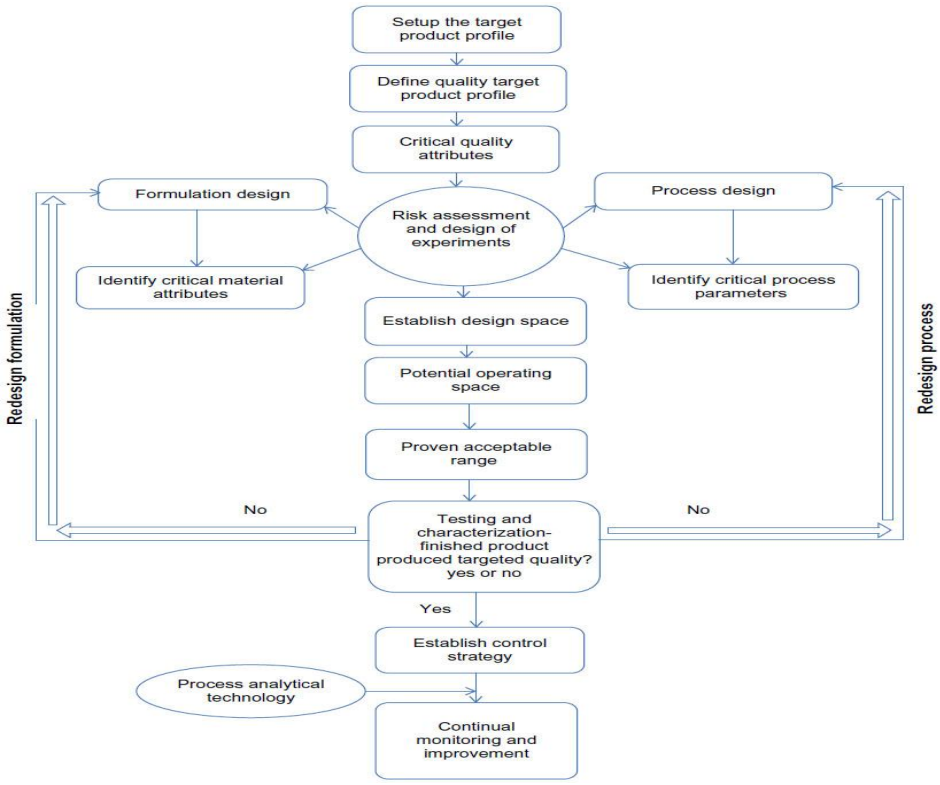

Fig no: 1 Flow chart of quality by design

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:

Tablet Characteristics

Identity

Assay and Uniformity

Purity/Impurity

Stability and

Dissolution

Table 2. Quality Target Product Profile (QTPP) for Generic Acetriptan Tablets, 20 mg

QTPP Elements		Target	Justification
Dosage form		Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strengths		20 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics		Immediate release enabling Tmax in 2.5 hours or less; Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	Identification		
	Assay		
	Content uniformity		
	Dissolution		
	Degradation product		
	Residual solvent		
	Water content		
	Microbial limit		
Container closure system		Container closure system qualified as suitable for this drug product.	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration/Concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and Cmax by 8-12%. The product can be taken without regard to food.
Alternative methods of administration		None	None are listed in the RLD label.

b. Identifying critical quality attributes

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

A critical quality attribute (CQA) is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." The identification of a CQA from the QTPP is based on the severity of harm to a patient should the product fall outside the acceptable range for that attribute.

All quality attributes are target elements of the drug product and should be achieved through a good quality management system as well as appropriate formulation and process design and development. From the perspective of pharmaceutical development, we only investigate the subset of CQAs of the drug product that also have a high potential to be impacted by the formulation and/or process variables. Our investigation culminates in an appropriate control strategy.

Table 3. Critical Quality Attributes (CQAs) of Generic Acetriptan Tablets, 20 mg

Quality Attributes of the Drug Product		Target	Is this CQA?	Justification
Physical Attributes	Appearance	Color and shape acceptable to the patient. No visual tablet defects observed.	NO	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odour	No unpleasant odor	NO	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process.
	Size	Similar to RLD	NO	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD.
	Score configuration	Unscored	NO	The RLD is an unscored tablet; therefore, the generic tablet will be unscored. Score configuration is not critical for the acetriptan tablet.
	Friability	NMT 1.0% w/w	NO	Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints.
Identification		Positive for acetriptan	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled

			by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay	100% w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
Content Uniformity (CU)	Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process variables impact content uniformity, so this CQA will be evaluated throughout product and process development.
Dissolution	NLT 80% at 30 minutes in 900 mL of 0.1 N HCl with 1.0% w/v SLS using USP apparatus 2 at 75 rpm	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.

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.

FDA suggest various tools that can be applied for QRM, among which the relevant ones are discussed below:

1. Failure mode effects analysis (FMEA)

FMEA is one of the most commonly used risk-assessment tools in the pharmaceutical industry. It is a systematic and proactive method to identify and mitigate the possible failure in the process. Failure modes represent any errors or defects in a process, material, design, or equipment. Once failure modes are established, FMEA tool evaluates the effect of these failures and prioritizes them accordingly. Risk control activities can then be performed to avoid such failures modes. Since FMEAs require a good understanding of cause and effects, a thorough process understanding is essential.

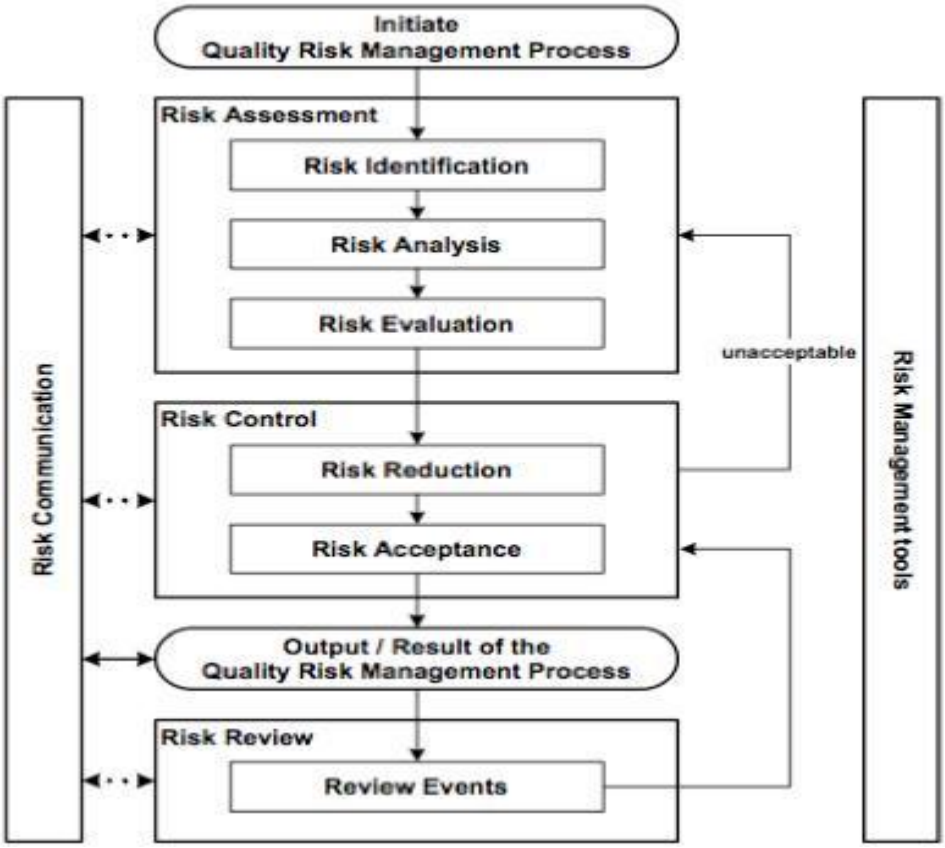

Fig 3 Overview of typical quality risk assessment process

2. Fault tree analysis (FTA)

The fault tree analysis (FTA) was first introduced by Bell Laboratories and is one of the most widely used methods in system reliability, maintainability and safety analysis. FTA is a deductive analysis approach for resolving an undesired event into its causes in a top down

fashion. Typically, assumed failures are listed at the top as main event and all of the associated elements in that system that could cause the event are listed as subsequent branches till the root condition or cause is identified. The results are represented pictorially in the form of a tree of fault modes and there relationship are described with logical operators like "AND", "OR", etc.

3. Hazard analysis and critical control points (HACCP)

HACCP provides detailed documentation to show process or product understanding through identifying parameters to control and monitor. The definition of hazard includes both safety and quality concern in a process or product. Examples of hazards within the pharmaceutical setting include environmental aspects of the facility (environmental conditions, hygiene aspects); material flow; manufacturing steps; personnel hygiene and gowning; and technical aspects relating to process design. HACCP consists of the following seven steps: (i) conduct a hazard analysis and identify preventive measures for each step of the process, (ii) determine the critical control points, (iii) establish critical limits, (iv) establish a system to monitor the critical control points, (v) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control, (vi) establish system to verify that the HACCP system is working effectively, (vii) establish a record-keeping system.

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.

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.

PHARMACEUTICAL QUALITY BY DESIGN TOOLS

Prior Knowledge

Although not officially defined, the term "prior knowledge" has been extensively used in workshops, seminars and presentations. In regulatory submissions, applicants often attempt to use prior knowledge as a "legitimate" reason for substitution of scientific justifications or conducting necessary scientific studies.

Knowledge may be defined as a familiarity with someone or something, which can include information, facts, descriptions, and/or skills acquired through experience or education. The word "prior" in the term "prior knowledge" not only means "previous," but also associates with ownership and confidentiality, not available to the public. Thus, for the purpose of this paper, prior knowledge can only be obtained through experience, not education. Knowledge gained through education or public literature may be termed public knowledge. Prior knowledge in the QbD framework generally refers to knowledge that stems from previous experience that is not in publically available literature. Prior knowledge may be the proprietary information, understanding, or skill that applicants acquire through previous studies.

Risk Assessment

ICH Q9 quality risk management indicates that "the manufacturing and use of a drug product, including its components, necessarily entail some degree of risk. The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient and the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk." The purpose of ICH Q9 is to offer a systematic approach to quality risk management and does not specifically address risk assessment in product development. However, the risk assessment tools identified in ICH Q9 are applicable to risk assessment in product development also.

The purpose of risk assessment prior to development studies is to identify potentially high-risk formulation and process variables that could impact the quality of the drug product. It helps to prioritize which studies need to be conducted and is often driven by knowledge gaps or uncertainty. Study results determine which variables are critical and which are not, which facilitates the establishment of a control strategy. The outcome of the risk assessment is to identify the variables to be experimentally investigated. ICH Q9.provides a nonexhaustive list of common risk assessment tools as follows:

- Basic risk management facilitation methods (flowcharts, check sheets, *etc*.)
- Fault tree analysis
- Risk ranking and filtering
- Preliminary hazard analysis
- Hazard analysis and critical control points
- Failure mode effects analysis
- Failure mode, effects and criticality analysis
- Hazard operability analysis
- Supporting statistical tools

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug product quality.

Mechanistic Model, Design of Experiments, and Data Analysis

Product and process understanding is a key element of QbD. To best achieve these objectives, in addition to mechanistic models, DoE is an excellent tool that allows pharmaceutical scientists to systematically manipulate factors according to a prespecified design. The DoE also reveals relationships between input factors and output responses. A series of structured tests are designed in which planned changes are made to the input variables of a process or system. The effects of these changes on a predefined output are then assessed. The strength of DoE over the traditional univariate approach to development studies is the ability to properly uncover how factors jointly affect the output responses. DoE also allows us to quantify the interaction terms of the variables. DoE is important as a formal way of maximizing information gained while minimizing the resources required. DoE studies may be integrated with mechanism-based studies to maximize product and process understanding.

When DoE is applied to formulation or process development, input variables include the material attributes (*e.g.*, particle size) of raw material or excipients and process parameters

(*e.g.*, press speed or spray rate), while outputs are the critical quality attributes of the in-process materials or final drug product (*e.g.*, blend uniformity, particle size or particle size distribution of the granules, tablet assay, content uniformity, or drug release). DoE can help identify optimal conditions, CMAs, CPPs and ultimately, the design space. FDA scientists have shown the use of DoE in product and process design in recent publications.

Process Analytical Technology

The application of PAT may be part of the control strategy. ICH Q8 (R2) identifies the use of PAT to ensure that the process remains within an established design space. PAT can provide continuous monitoring of CPPs, CMAs, or CQAs to make go/no go decisions and to demonstrate that the process is maintained in the design space. In-process testing, CMAs, or CQAs can also be measured online or inline with PAT. Both of these applications of PAT are more effective at detecting failures than end-product testing alone. In a more robust process, PAT can enable active control of CMAs and/or CPPs, and timely adjustment of the operating parameters if a variation in the environment or input materials that would adversely impact the drug product quality is detected.

Application of PAT involves four key components as follows

- Multivariate data acquisition and analysis
- Process analytical chemistry tools
- Process monitoring and control
- Continuous process optimization and knowledge management

Multivariate data acquisition and analysis requires building scientific understanding about a process and identifying critical material attributes and process parameters that affect product quality and integrating this knowledge into the process control, which is essentially the same as the process understanding in the context of QbD. Process analytical chemistry tools provide real-time and *in situ* data about the status of the process. Multivariate data analysis takes the raw information from the PAT tools and connects it to CQAs. Based on the outcome of the data analysis, process controls adjust critical variables to assure that CQAs are met. The information collected about the process provides a basis for further process optimization. Studies in FDA laboratories indicated the promise of several PAT tools and chemometric approaches.

CONCLUSION

The goals of implementing pharmaceutical QbD are to reduce product variability and defects, thereby enhancing product development and manufacturing efficiencies and post-approval change management. It is achieved by designing a robust formulation and manufacturing process and establishing clinically relevant specifications. The key elements of pharmaceutical QbD can include the QTPP, product design and understanding, process design and understanding and scale up, control strategy and continual improvement. Prior knowledge, risk assessment, DoE and PAT are tools to facilitate QbD implementation. Finally, product and process capability is assessed and continually improved postapproval during product lifecycle management.

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