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QUALITY BY DESIGN: ITS APPLICATIONS

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ABSTRACT

Quality design (QBD) is a modern and systematic approach for product development and quality of pharmaceuticals. Quality by design is a concept first outlined by well known quality expert Joseph M. Juran. QBD is best key to build a quality in all pharmaceutical products, it is important to identify desire product performance report.QBD has it perspective to contribute the drug design, development, and manufacture of high quality drug product. Now-a –days the concept of Qbd can be extended to analytical techniques. In this analytical concept it is essential to define desire product performance profile, analytical target profile [ATP], identify critical quality attributes throughout designing and development process. The review aimed to identify implementation of QBD in analytical procedure validation. The outcomes of organized analytical process development and validation understand of critical quality attributes, risk assessment and outlining design space, and control strategy. The Quality by design is based on the ICH guidelines Q8 for pharmaceutical for development, Q9 Quality risk management, Q10 for pharmaceutical quality systems.

KEYWORDS: Quality target product profile, critical quality attributes, risk assessment, control strategy.

1. INTRODUCTION

Quality

Quality is "standard or suitability for intended use. "The term includes such attributes as the identity, potency, and purity.[1]

Quality by design

Pharmaceutical industries are alert on product quality, safety, and efficacy. Product quality has been increasing by implement scientific tool such as QbD. They minimize the risk by increasing output and quality. QbD approach is implemented successfully in formulation development. Regulatory authorities are always proposing the implementation of ICH quality guidelines Q8 to Q11.[2,3]

QBD is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.[4]

It means that, design and develops the formulation and manufacturing process to make sure predefined product quality and requires product and process variables influencing product quality. It is a systematic process to build the quality in to final product. Critical quality attributes will determine the level to which any variation can impact quality of final product.[5]

1.1 Objectives

- To facilitate innovation and continuous improvement throughout the product life cycle.
- To achieve meaningful product quality specifications that is based on clinical trials.
- To provide regulatory flexibility for specifications setting and post-approval changes.
- To increase product capability and reduce variability.
- To increase product development and manufacturing efficiencies.
- To enhance root cause analysis and post-approval change management.[6]

1.2 History

The concept quality by design was described by well known quality expert "Joseph Moses Juran". He believed that quality could be planned and that most quality associated problems have their origin in the way which quality was planned in first place.[7] His discovery of "designed in" concept, is used in QBD for optimization of product.

In the pharmaceutical quality improvement FDA announced proposed amendments to "current good manufacturing practices (cGMP) in 2002.

FDA released "Guidelines on General principles of Process validation in 1987.

- ICH (1999): It defines concepts of quality

Assist the establishment of global specification for new drug substances.

- FDA (2004): Outlines of QBD concepts.

It encourages science-based policies and innovation in pharmaceutical development and manufacturing.

- FDA (2004): It defines the industrialization process.

Activities related to product design, process design, and technology transfer.

- FDA (2005): Implementation of QBD for more systematic approach.

The key framework guidance documents for implementation of QBD are ICH (International conference on harmonization.

- ICH Q8: Pharmaceutical development

It focuses on the concepts of Common Technical Documents (CTD) and promotes the concepts of QBD. It approaches quality risk management principles.

- ICH Q9: Quality risk managements

It is a systematic approach to conduct risk assessment and manage the risk.

- ICH Q10: Pharmaceutical quality system

It focuses on regulating the quality management systems (QMS) into industry

- ICH Q11: Development and Manufacturing of drug substances

Its focuses on development and manufacturing process of both chemical, biological drug substance.

The use of QBD strengthened in 2007, when FDA received up to 5000 supplements. It was actually striking rising in the number of supplements to applications of NDA's, BLAs, ANDAs.[8]

1.3 Elements of Pharmaceutical Development

The pharmaceutical development provides a complete understanding of the product and manufacturing process for reviewers and inspectors. To design a quality product and its manufacturing process to consistently deliver the intended performance of product is the aim of pharmaceutical development.

Different elements of pharmaceutical development include:

- Defining an objective
- Determination of critical quality attributes(CQAs)
- Critical process parameters
- Risk assessment
- Development of experimental design
- Control strategy
- Continuous improvement.[9]

Fig. 1: Elements of pharmaceutical development.

Objective

Quality target product profile

A drug product that will be achieved to ensure the desired quality, safety, and efficacy.The QTPP is specified only for finished product. The QTPP will help to identify critical quality attributes like potency, purity, pharmacokinetic profile, shelf-life and sensory properties. The QTPP forms basis of design for development of a product.

- Route of administration
- Dosage form
- Dosage strength
- Container closure system
- Pharmacokinetics
- Drug product quality criteria (purity, sterility, stability, drug release)

QTPP is a natural extension of TPP of product quality. RLD (Reference listed drug) can readily determine the generic drug of QTPP. [10]

QTPP could include critical and non-critical elements.

Critical quality attributes

A CQA is a physical, chemical, biological, microbiological property (or) characteristic that should be within appropriate limit, range or distribution to ensure the desired product quality.[11]CQA generally associated with excipients, drug substances, intermediate drug product. CQAs of pharmaceutical product are typically those that affect product purity, strength, drug release and stability for solid dosage forms and for parental they are sterility and clarity. The product that affects additionally includes particle size, and bulk density.[12]

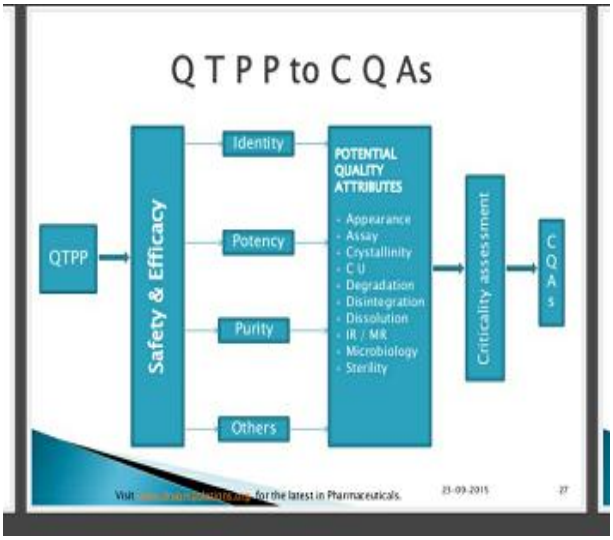

Fig. 2: QTPP TO CQAs.

Potential drug product CQAs are used to guide product and process development. List of potential CQAs can be increased by knowledge drug substance and process understanding. Impurities are important class of potential drug substance CQAs. The quality attributes should control the product in its limits and product should be meet its intended safety, efficacy, and stability and performances. It means all the factors which affect final quality and safety should be controlled.[13]

Critical Material Attributes and Critical process parameters

Material attributes

Materials: raw materials, starting materials, reagents, solvents, processing aids, intermediate, and packaging, labeling materials.

In identification of CQAs of drug product, the assessment of linkage between drug substances to drug product is necessary. To understand material attributes most of excipient functionality is important to performances. The selection of salt, solid forms, particle size and morphology also impact critical quality attributes.[14]

Material attributes can be quantified and typically fixed but sometimes can be changed during further processing. Examples: Impurity profile, porosity, specific volume, sterility.[15]

Critical process parameters

Critical process parameter is one shoe impact on critical quality attributes. It's should monitored or controlled to ensure the process produces the desired quality. A pharmaceutical manufacturing process usually consists of series of unit operations (like mixing, milling, granulation, drying etc) to produce a desired quality product.[16]

CPPs are responsible for ensuring the CQAs and it is identified by list of potential CPPs using risk assessment. There are 3 categories of parameters:

1. **Unclassified parameters:** The criticalities of unclassified parameters are unknown. The additional data are needed to classify an unclassified parameter as critical or non-critical.
2. **Critical parameters:** A parameter is critical when a realistic change in that parametercan cause the product to fail to get the QTPP.
3. **Non-critical parameters:** No failure in QTPP observed in the potential operating space and no interactions with other parameters in established suitable range.

Examples for CPP: Temperature, addition rate, cooling rate, rotation speed, pH, agitation.[15]

Risk assessment

Risk is defined as the combination of probability of occurrence of harm or the severity of harm. It helps to increase quality of method.[17] Risk assessment means science-based process used in quality risk assessment and it can identify material attributes and process parameters that affect the product CQAs. Risk assessment can impact product quality, initial experimental data. Relative risk of drug substance is attributes was ranked as high, medium, low.

Quality risk management is systematic process for the risk management, risk control, risk communication, and risk review to the quality of the product across the product across the product life cycle.[18] Risk assessment is useful for effective communication between FDA and industry, research, development and manufacturing multi manufacturing sites within company. Risk management for excipients to determine shelf-life can be done by statistical parameters.

Principle

- Scientific knowledge based evaluation of the risk to quality which eventually links to protection of patient.
- Adequate effort should be taken formality and documentation of the quality risk management process should be done with the level of risk involved.

Methods

1. Failure mode effects analysis(FMEA)
2. Failure mode effect and criticality analysis(FMECA)
3. Fault tree analysis(FTA)
4. Hazard analysis and critical control points(HACCP)
5. Risk ranking and filtering(PHA)
6. Supporting statistical tools.[19]

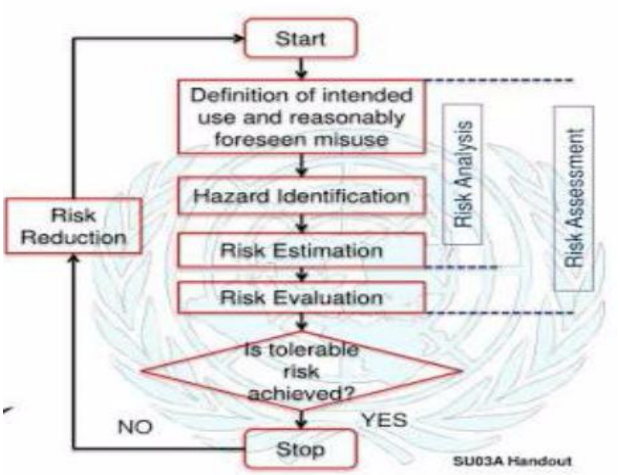

Fig. 3: Model of quality risk management.

Design space

A design space is a multidimensional combination and interaction of input variables that have been demonstrated to provide assurance of quality. The relation between the process inputs and critical quality attributes is described in the design space. Risk assessment can guide to understand the linkage and effect of process parameters & material attributes on product and range for variables with in which consistent quality can be achieved. These parameter or attributes are selected for addition in the design space. Analysis of historical data can provide the basis for establishing a design space. How a design is developed, it is expected that operation Within the design space will result in a product should meet its quality. [20]

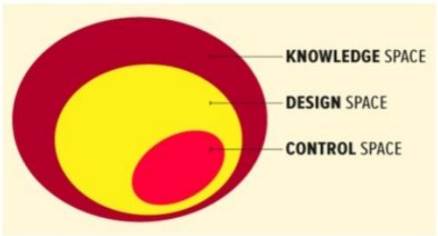

Fig. 4: Design space.

The applicant can choose to establish independent design space that spans multiple operations. A design space, the applicant should consider the type of operation flexibility desired. A design space can be developed at any scale. Design space is proposed by applicant is subjected to regulatory assessment and approval to ICH Q8.once design space is approved, then regulatory post-approval change requirement will be simplified inside space. When design space is defined then we are able to plan control process.[21]

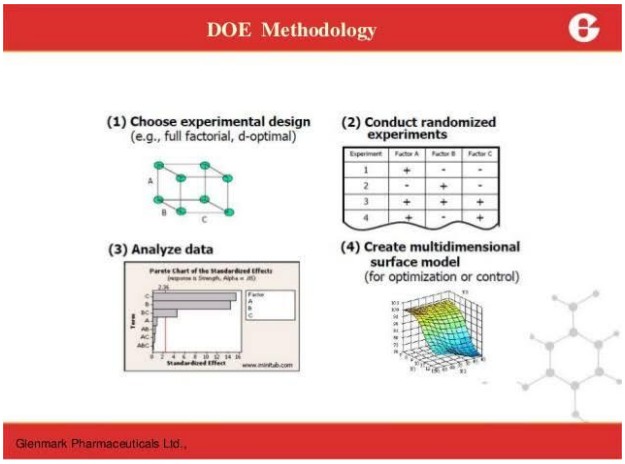

Fig. 5: Design space methodology.

Control strategy

Control strategy is defined as, "A designed set of control, derived from current product and process understanding that assures process performance and product quality. Control strategy is required to ensure that material and process are within the expected lower and upper limits. It helps in avoiding defect and maintains desired quality.[22] The control space should be in design space. QBD gives traces on reproducibility and robustness, and process capability index expression reproducibility of process.

Process capability index (CpK) = upper limit of specification-lower limit of specification/6 standard deviation.[7]

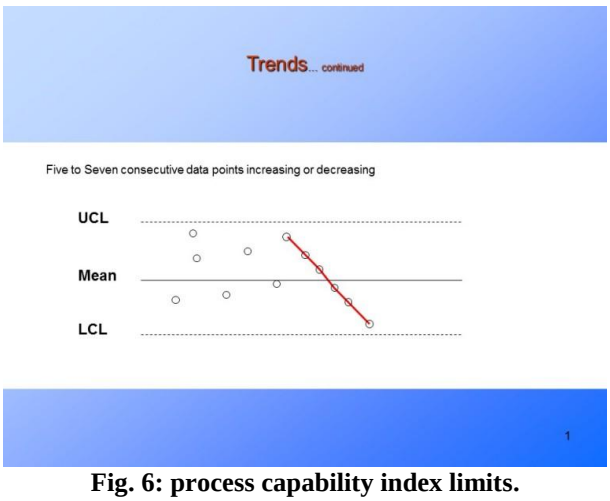

Fig. 6: process capability index limits.

Control strategy may include input material control, process controls, and monitoring, design space to final product specification used to ensure consistent quality.[10]

Elements of control strategy

- Procedural control
- In-process controls
- Batch release testing
- Process monitoring
- Comparability testing
- Constancy testing

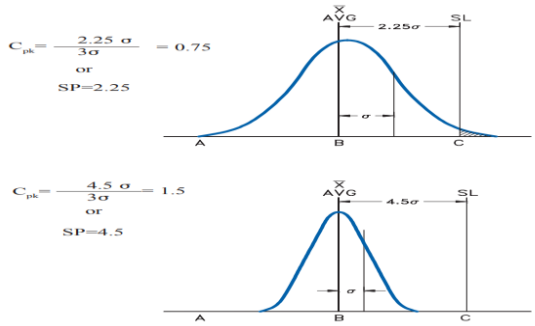

Fig. 7: Process capability Index (C_{pK}).

The control strategy in the QBD standard is established via risk assessment that takes in to account the critically of the CQAs. Example: Impurity fate mapping (IFM) in which raw material and process impurity sources are identify and their fate mapped throughout process. Remove impurity is an essential element of control strategy. [19]

Product life cycle &continuous improvement

Product quality can be improved throughout the product life cycle. Companies have opportunities to evaluate modern approach to improve product quality. Process performance can be monitored to make sure consistency in quality. Periodic maintenance can be done within the company‘s own internal quality system.

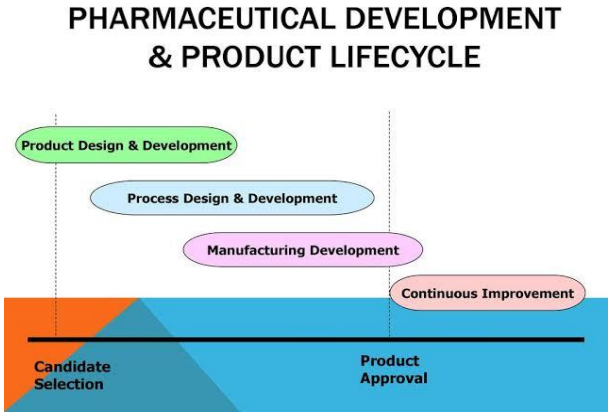

Fig. 8: product cycle.

Continuous improvement is an essential element in modern quality system. QBD focuses on quality into the product, as well as continuous process improvement-reduction of variability.

The backbone for continuous improvement is Pharmaceutical Quality System (PQS). It helps to “identify and implement appropriate product quality improvements, process, improvements, variability improvements, thereby increasing the ability to fulfill the quality.[22]

Fig. 9: Continuous improvement.

Advantages

- Patient safety and product efficacy are focused.
- It offers robust method and process
- Business benefit are also driving force to adopt QBD.[7]

Current vs. QBD Approach to pharmaceutical development.

Current Approach	QBD Approach
• Quality assured by testing and inspection • Data intensive submission- disjointed information without “big picture” • Specifications based on batch history • “Frozen process”, discouraging change • Focus on reproducibility-often avoiding or ignoring variations.	• Quality built into product and process by design, based on scientific understanding • Knowledge rich submission- showing product knowledge and process understanding • Specification based on product performance requirements • Flexible process with design space allowing continuous improvement • Focus on robustness- control variation [23]

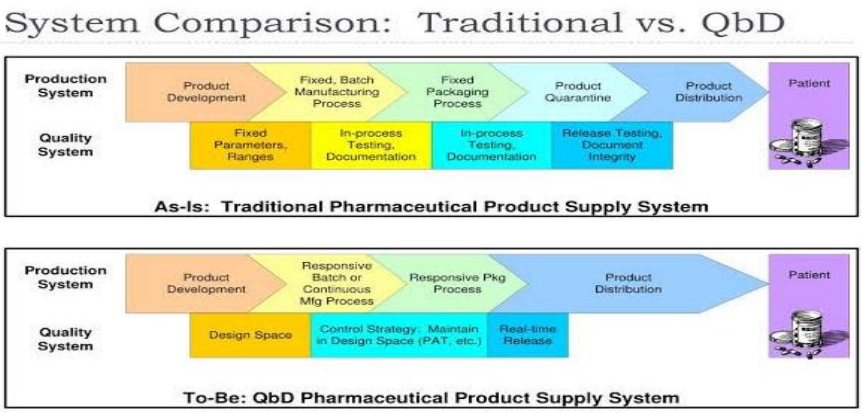

Fig. 10: System comparison Traditional vs. QBD.

4. QBD in analytical method development and validation

Analytical procedure is fully integrated into the QBD paradigm and is an essential step in developing technique which used for applications. The main aim is to define the purpose of the analytical method begins validated and its measure of fitness. A method validation is a threestage approach.

Method design defines requirements and conditions and identifies critical controls.

Method qualification confirms that the method is capable of meeting its design intent.

Continued method verification gains ongoing assurance to ensure that the method remains in a state of control during routine use.

Following steps are involved in QBD to an analytical approach:

1. Analytical target profile
2. Determination of critical quality attributes(CQAs)
3. Risk assessment
4. Designing and implementation of a control strategy
5. Management of product life cycle and continual improvement.[24]

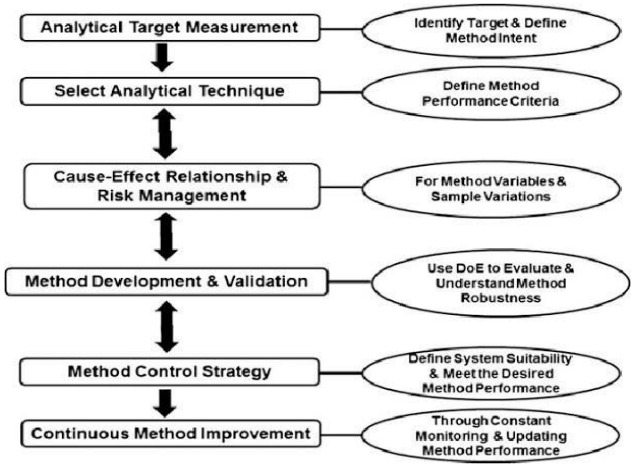

Fig. 11: Quality in analytical method development.

4.1 Potential benefits of adopting QBD for analytical method

- The development method will be more robust which gives greater level of confidence in case of variation in conditions.
- This approach gives greater transfer success when method is transferred from research level to quality control department.
- It helps for enhanced understanding of the method.
- Design space concept avoids the post-approved changes which may cause to pay a high cost for any of the firm.
- It provides greater compliance with regulatory authorities.[7]

5. Drugs that marketed based on quality by design system

- Lovastatin
- Lidocaine & Prilocaine (Cream)
- Proliposome Of Lopinavir (Oral formulation)
- Carbopol Transgel (Diabetic tablet)

Applications

The basic concept of QBD is "The quality is tested into the product, but it should be built into it." During development of analytical methods, same QBD principle can be applied to the development of analytical method. Various quality and statistical tools and methods, such as statistical designs and experiments, multivariate statistics, statistical quality control have been comprised in QBD. The main goal for changing from quality by testing is to accelerate the understanding of the product such that product quality, processes efficacy, and regulatory flexibility can be attained.

QBD can be applied for various analytical methods include

- Chromatographic techniques like HPLC(High performance liquid chromatography)
- Hyphened technique like LC-MS
- Karl-fisher titration for determination of moisture content.
- Analysis of genotoxic impurities.[25]

6. Regulatory perspective of analytical QBD

In a QBD concept, the regulatory burden is less because there and wider ranges and limits do not require prior approval. Implementation of AQBD is expected to strengthen the concept of "right analytical at right time" it plays an important role in product development cycle. FDA has been approved a few new drug applications based on AQbD and it is an important benefits of QBD in analytical method development.[26]

7. CONCLUSION

Quality by design is an essential part of modern approach pharmaceutical quality.QBD has gain importance in the area of pharmaceutical process like drug development, formulation, analytical method and pharmaceuticals. The main reason for adopting of QBD is the regulatory requirements. Pharmaceutical industry needs a regulatory compliance so as to get their product approved for marketing. The applications of implementing AQbD in process development andvalidation understand of critical quality attributes, risk assessment, and design space. Control strategy and continual improvement is possible for further investigation. It also meets FDA requirements for pharmaceutical quality management system. The most common methods are more robust and rugged, and thus survive the challenges of long-term usage in product life cycle.

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