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REVIEW ON HISTORICAL BACKGROUND, KEY ASPECTS, TOOLS, APPLICATIONS AND CHALLENGES ADOPTING IN QUALITY BY DESIGN (QbD).

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ABSTRACT
Quality by Design is the modern approach for quality of pharmaceuticals. concept of "Quality by Design" (QbD) gaining much attention among pharmaceutical industries for maintaining Quality. The principles of quality have been described by the ICH guidelines: Q8 Pharmaceutical development, Q9 Pharmaceutical quality risk management and Q10 Pharmaceutical quality system. This paper gives idea about the Pharmaceutical Quality by Design (QbD) and describes use of Quality by Design to ensure quality of Pharmaceuticals. It is a scientific approach that helps to build in quality into the product rather than mere testing of the final product. For the implementation of QbD various tools are needed to be used which have been described briefly. Risk assessment approaches, process analytical technology tools and mathematical, statistical and continuous improvement tools are important elements of quality by design, which mainly focus on the identification of critical parameters and defining a design space statistically. The basic principles of these three ICH guidelines with regard to quality of pharmaceutical products have been briefly discussed.

KEYWORDS: Quality by Design (QbD), Target Product Quality Profile (TPQP), Critical Quality Attribute (CQA), Critical Process Parameter (CPP), Quality Risk Management (QRM).

INTRODUCTION[3]

Quality

In Quality by Design, Quality is important word. So Quality is "standard or suitability for intended use." This term includes such attributes as the identity, potency, and purity.

Quality by design

Pharmaceutical industry are alert on product Quality, Safety, and Efficacy. Product quality has been increasing by implement scientific tools such as QbD (Quality by Design).

According to ICH Q8 guidelines, QbD is defined as, "A systematic approach to development that begins with predefined objectives & emphasizes product, process understanding & process control, based on sound science & quality risk management."[4] It means that, design & develop the formulation & manufacturing process to make sure predefined product quality.

A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes.

Benefits of QbD

For industry:

- Better understanding of the process.
- Less Batch failure.
- Ensure better design of products with less problems in manufacturing.
- Allows for continuous improvement in products & manufacturing process.

For Fda

- Enhances scientific base for analysis.
- Provide better consistency.
- Provide for more flexibility in decision making.
- Ensures decisions made on science & not on observed information.

Historical background[2]

In 2007, the FDA received a total of 5000 proposals for new drug applications (NDAs) and biological license applications and abbreviated new drug applications (ANDAs). „Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach" was launched by the FDA in August 2002.

A further guidance on process analytical technology (PAT) was released as part of the „cGMPs for the 21st

Century" initiative, In March 2004, the FDA launched The Critical Path Initiative (CPI) to address the steep decline in the number of innovative pharmaceutical products submitted for approval. The national strategy was to modernize the pharmaceutical sciences through which FDA-regulated products are developed, evaluated, manufactured and used.

This prompted to the publishing of a guideline to aid manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency"s current thinking for cGMP regulations.

Good manufacturing practices for the 21st century have been continually evolving as the ICH quality initiatives have been adopted.

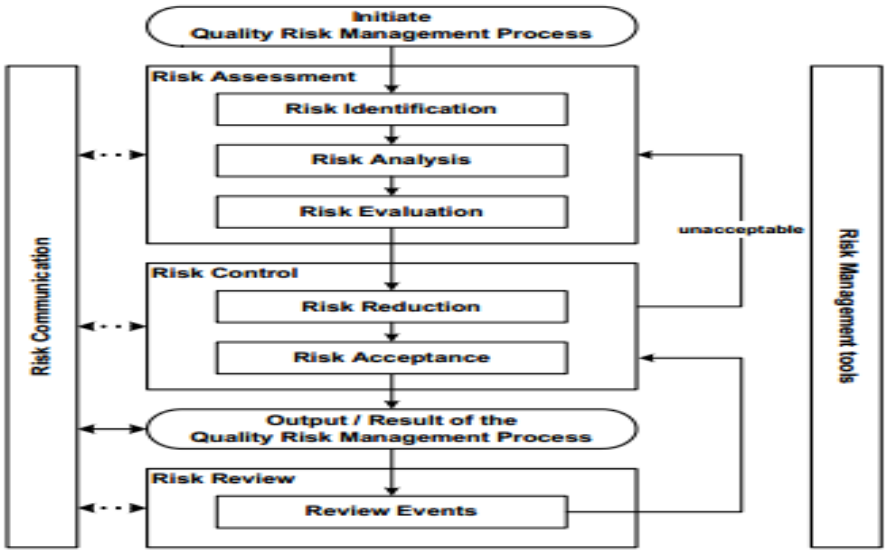
ICH Q8, Q9, Q10 Guidelines: foundation of QbD[2]

ICH Q8 Pharmaceutical development

provides information on how to present knowledge gained when applying scientific approaches and quality risk management for developing and manufacturing a product It is in the ICH Q8 annex that QbD is clearly 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" Two other important terms for discussing QbD were also defined in ICH Q8; Design Space and PAT. Design space is defined 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".

ICH Q9 Quality risk management

Provides general guidance and references for some of the primary tools used in risk assessment. The purpose of ICH Q9 was to offer a systematic approach to quality risk management.



Quality risk management process.

ICH Q9 the following tools are suggested for risk management in the pharmaceutical industry:

- Flow charts;
- Check sheets;
- Process mapping;
- Cause and effect diagrams;
- Failure mode effects analysis (FMEA);
- Failure mode effects and criticality analysis;
- Fault tree analysis;
- Hazard analysis and critical control points;
- Hazard operability analysis;
- Preliminary hazard analysis;

ICH Q10 Pharmaceutical quality system

Describes a comprehensive model for an effective pharmaceutical quality system that is based on International Organization for Standardization (ISO) quality concepts, includes applicable cGMP regulations, and complements ICH Q8 and ICH Q9.

The Pharmaceutical Quality System had described four key elements:

- A process performance and product quality monitoring system;
- A corrective action and preventive action system;
- A change management system;
- Management review of process performance and product quality.

Adoption of ICH Q10 should "facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

ICH Q10 Pharmaceutical quality system model.

Key aspects of QBD[1,2,4]

1. The target product quality profile (TPQP)

TPQP 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".

TPP forms the basis for product design in the following way10.

- Dosage form
- Route of administration
- Strength, maximum and minimum
- Release/delivery of the drug
- Pharmacological characteristic
- Drug product quality criteria
- Pharmaceutical elegance

2. Critical Quality Attribute

Once TPQP 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 isdone through risk assessment as per the ICH guidance Q9. CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability. CQAs for other delivery systems can additionallyinclude more product specific aspects, such as aerodynamic properties for inhaledproducts, sterility for parenteral, and adhesion properties for transdermal patches.

3. Critical Process Parameter

Critical process parameters (CPPs) are defined as "parameters whose variability have an impact on a CQA Process robustness is defined as theability 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 The most widely accepted formula for process capability is six sigma. Process capability index (CpK) is

$$\textbf{CpK} = \frac{\text{Upper limit of specification - Lower limit of specification}}{6 \text{ standard deviation}}$$

If the CpK is significantly greater than one, the process is defined capable. If it is low five step procedures to progressively reduce the variability of the process. These fivesteps are:

I. **Define:** The intended improvement should be clearly stated

II. **Measure:** The critical product performance attribute should be measured to see if they are out of specification and used to the sigma level of the process.

III. **Analyze:** When the sigma level is below the target, steps should be taken to increase it, starting by identifying the most significant causes of the excessive variability.

IV. **Improve:** The process should be redesigned and/ or process controls should be incorporated to eliminate or attenuate the significant toot causes of variance.

V. **Control:** The improved manufacturing process should be evaluated and maintained.

4. Risk Assesment

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. The initial list of potential parameters which can affect CQAs can be quite extensive but can be reduced and prioritized by quality risk assessment (QRA). QRA is a science based process that can aid identification of CPPs and thus eliminating risk, resulting in high confidence that the analytical method will meet

the QTTP under all conditions of use. Thus, a large number of parameters can actually be safely eliminated by use of QRA tools.

5. Design Space

The ICH Q8(R2) States that the design space is 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 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.

6. Control Strategy

The ability to evaluate and ensure the quality of in-process and/or final product based on process data which typically include a valid combination of measured material attributes and process controls. ICH Q8(R2). Control strategy is defined as "a planned set of controls, derived from current product and process understanding that assures process performance and product quality". 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)9.

7. Life Cycle Management

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.

Tools applied in qbd appr oach[5,6]

Design of experiment (DoE)

This is a systematic approach applied to conduct experiments to obtain maximum output.

Design of experiments

Screening

Designs applied to screen large number of factors in minimal number of experiments to identify the significant ones. Main purpose of these designs is to identify main effects and not the interaction effects. optimization: Experimental designs considered to carry out optimiztion are mainly full factorial design, surface response methodology (e.g. Central composite, Box-Behnken), and mixture designs. These designs include main effects and interactions and may also have quadratic and cubic terms require to obtain curvature.

Risk assessment methodology

Cause and Effect Diagrams (fish bone/Ishikawa): This is very basic methodology to identify multiple possible factors for a single effect (Figure 3). Various cause associated with single effect like man, machine, material, method, system, and environment need to be considered to identify root cause.

Process analytical technology (PAT)

Control Strategy: Assurance of product quality during intermittent steps using Process Analytical Technology (PAT) is recommended by regulatory authorities, which is yet to be extensively accepted by the pharmaceutical industry over conservative methodologies. It involves advanced online monitoring systems like NIR (Near IR), Handheld Raman Spectrometer, Online Particle Size Analyzer etc. We are experienced in appliction of NIR and Raman Spectrometer to monitor processes viz. blending and wet granulation. These technologies further make assurance of continuous improvement in process and product quality through its life cycle

Steps for pharmaceutical Qbd implementation[5]

As a general rule, the practical implementation of QbD in the development of new pharmaceutical products can go through the following steps

1. Define the desired performances of the product and identify the QTPPs;
2. Identification of the CQAs;
3. Identification of possible CMAs and CPPs;
4. Setup and execution of DoE to link CMAs and CPPs to CQAs and get enough information of how these parameters impact QTPP. Thereafter, a process Design Space should be defined, leading to an end product with desired QTPP;
5. Identify and control the sources of variability from the raw materials and the manufacturing process;
6. Continually monitor and improve the manufacturing process to assure consistent product quality.

So far, most of the pharmaceutical unit operation processes can be optimized by applying the concept of QbD

Application of quality by design[3]

Quality by design (QbD) – A comprehensive systematic approach to pharmaceutical development and manufacturing

Advancement in the pharmaceutical development and manufacturing by Qbd can be explained against traditional approach.

Aspects	Traditional	QbD
Pharmaceutical development	Empirical	Systematic ,multivariate experiment
Manufacturing Process	Fixed	Adjustable within design space; opportunities for innovation
Process control	In process testing for go/on-go offline analysis wide or slow response	PAT utilizes for feedback and feed forward at real time
Product specification	Primary mean of quality control ; based on batch data	Part of the overall control strategy, based on the desired product performance
Control Strategy	Mainly by intermediate; product and end product testing	Risk based ; controlled shifted up stream, real time realease
Lifecycle Managment	Reactive time problem and oos post approval changes needed	Continual improvement enable within design space

In Pharmaceutical Development

To design a quality product and a manufacturing process to consistently deliver the intended performance of the product.

The challenges of adopting QbD[9]

Despite the many financial and operational benefits of QbD, and even with the new FDA recommendations, not all companies have adopted this approach. As the saying goes "you either pay now, or pay later." Implementing QbD beginning at the development phase requires a dedicated, disciplined, and sustained commitment by an organization. Understanding the effort necessary to implement QbD is a key component to successful adoption. Some of the most common barriers to adoption include:

- Insufficient understanding of the process and its benefits
- Organizational resistance to change
- Denial of the need ("Our process is under control")
- Competing priorities
- Lack of resources and expertise in QbD.6

When you consider the tremendous potential financial gain, faster time to market, process improvements, and quality assurance generated by a successful implementation of QbD, these obstacles seem to pale in comparison.

CONCLUSION

QbD is increasingly becoming an important and widely used technique in pharmaceutical product development. The major objectives with regard to quality issues are addressed by the ICH guidelines. These are Q8 Pharmaceutical development, Q9 Pharmaceutical risk management and Q10 Pharmaceutical quality systems. The QbD approach leads to enhanced understanding, well defined system and regulatory flexibility. 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. This approach allows the establishment of priorities and flexible boundaries in the process. As such QbD is becoming a promising scientific tool in quality assurance in pharmaceutical industry.

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