GMP Training Systems, Inc.

Creators of the GMP Ready-to-Use Training System™

Quality by Design Boot Camp
Mitigate the Risk in Your Drug Manufacturing Processes

Learning Objectives

Upon completion of this workshop, participants will be able to:

- Understand Risk-Based GMP Compliance and FDA, ICH and ASTM Approaches
- Review Strategies for Defining Risk, Risk Factors and Risk Prioritization
- Understand the Basic Fundamentals and Approach of QbD
- How to use Design of Experiments (DoE) to Provide Regulatory Flexibility for Specification Setting and Post-approval Changes
- Use QbD to Mitigate Product Risk in Engineering Drug Manufacturing Operations
- Understand the Connection Between QbD and Process Analytical Technology (PAT)
- Implement the Concept of Innovation and Continuous Improvement throughout the product life cycle.

Who should attend

Professionals and technicians who should attend include:

- R & D scientists involved in process/product development and implementation
- Process engineers and chemists working in development and operations
- Pilot plant operations engineers, and scientists
- Technology transfer mangers
- Regulatory affairs personnel
- Quality assurance professionals
- Validation professionals
- Personnel responsible for GMP Compliance

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Day One

1. **Overview – Science and Risk based compliance**; this presentation will review the background and guidance dealing with risk based GMP compliance and the various approaches suggested by FDA, ICH, and ASTM to mitigate risk and ensure proper compliance is achieved. The documents that will be reviewed include:
    a. FDA Guidance "Pharmaceutical CGMP for the 21st century – A Risk-based Approach" and its implication. Additionally subsequent progress reports issued by the FDA regarding suggested approaches to mitigate risk will be discussed
    b. Review ICH Q8, Q9, Q10, and ASTM Standard E2500
    c. How does QbD fit within the big picture - ICH Q8
    d. What is meant by Product Life Cycle
    e. The jargon and acronymm definitions

2. **Risk and risk levels;** A presentation focused on defining risk, risk factors, and risk prioritization.
    a. Review ICH Q9 and Risk based Compliance principles.
    b. Defining risk factor levels and Risk Priority Number (RPN)
    c. Discuss the concept of "Action Commensurate with the Level of Risk"
    d. Risk Based Compliance and how to use the RPN to prioritize mitigation efforts and resource utilization.
    e. Outline a suggested risk assessment form.

3. Review of answers to initial questionnaire. Display answers to entire class.

4. ***Exercise***: Risk causing scenarios will be detailed and attendees will be guided, using a risk assessment form, through the appropriate steps required to define an RPN for each scenario.

5. **The basic approach and fundamentals of QbD;** A presentation focused on the fundamentals.
    a. Review ICH Q8 and ASTM E2500 to understand the QbD concept.

b. Define the QbD systematic process/approach. Discuss the need for User Requirement Specifications (URS). Learn about the Ishakawa Fishbone diagram and how it is developed. Discuss using root cause analysis techniques to identify risk factors. Review and discuss the principles of Design Of Experiments (DOE), Knowledge Space (Science base), Design Space (DS), the Normal Operating Space (Range)/Control Space (Range), and Design Reviews and how these can be used to support QbD implementation.
c. Present a step-by-step QbD implementation roadmap.

6. ***Exercise***: A User Requirement Specification (URS) will be defined and the attendees as a group will develop a Fishbone diagram to address developing a design to address the requirement.

Day Two

Discussion and recap of day one

7. **Design of Experiments:** The presentation will discuss the concepts associated with Design Of Experiments (DOE) or experimental design. Although DOE is a branch of statistics, this will not address the statistical methods associated with the approach. Rather it will present an overview of the subject in simple and understandable language without encumbering the discussion with involved statistical discussion.

   We will review the definition of DOE, its history and historical application and then we will review the application of DOE as part of developing responses to questions such as:
   - What are the key factors in a process,
   - What are the process settings that would deliver acceptable product quality with minimum variation, and
   - What are the interactions between the various variables associated with the process and their importance?

The presentation will discuss the concept associated with the Fisher methodology for DOE. These are comparison, randomization, replication, blocking, orthogonality, and factorial design. These concepts will be discussed individually in sufficient detail to give the uninitiated a feel for the capabilities and complexity of applying DOE in engineering and science. We will also present several examples detailing how to apply some of these concepts individually or in combination.

8. **Using QbD to mitigate product risk in engineering drug manufacturing operations**.

   Designing a drug manufacturing operation so as to minimize or eliminate the potential risks associated with the eventual operation can be achieved using an established systematic approach. Good Engineering Practices (GEP) and the principles of Quality by Design (QbD) represent the current FDA thinking to achieve such objectives. Applying QbD principals during the engineering of the facility and process (operation) for producing a drug product requires good scientific understanding of both the product's characteristics and the processing approach. Understanding the potential risks associated with the proposed operation requires utilizing Subject Matter Experts (SME) and risk analysis techniques. GMP principles must also be addressed by the eventual design thus ensuring process consistency.

9. ***Exercise*:** The entire group will have an open discussion of approaches to be taken to mitigate the risk associated with several real life design related issues.

   Did everyone get their questions answered? What questions remain?

10. **QbD, Process Analytical Technology (PAT) and the concept of continuous improvement.**

In this presentation we will review the connection between QbD and PAT. QbD is fundamentally based on identifying the correlation between Critical Quality Attributes (CQA) for the product and Critical Processing Parameters (CPPs). This information is usually identified using, process development information, experiments, data collected from the process, and previous knowledge. Once this information is well defined, it can be used to develop the required control strategies to ensure that quality is built into the design. Additionally this information is valuable in developing the models which could be used to implement PAT for the operation. Using PAT and collecting data throughout the product life cycle would allow for continuous process improvement and real time product release. We will explore the advantages of properly defining design space in regulatory applications.

11. **Open Discussion - A look at the future**:
    a. Ensure all questions are answered
    b. QbD is one of the tools that allows industry to build quality in the product and improve its compliance quotient.
    c. What is driving the concept – Technological advances and the need to reduce cost are obvious drivers; What else?
    d. Are changes to GMP regulations needed to accommodate real time release and risk based compliance.
    e. Verification instead of Qualification and the concept of continuous validation.