

2021 Virtual Conference: Culture of Quality Foundations of a Functioning Quality Management System

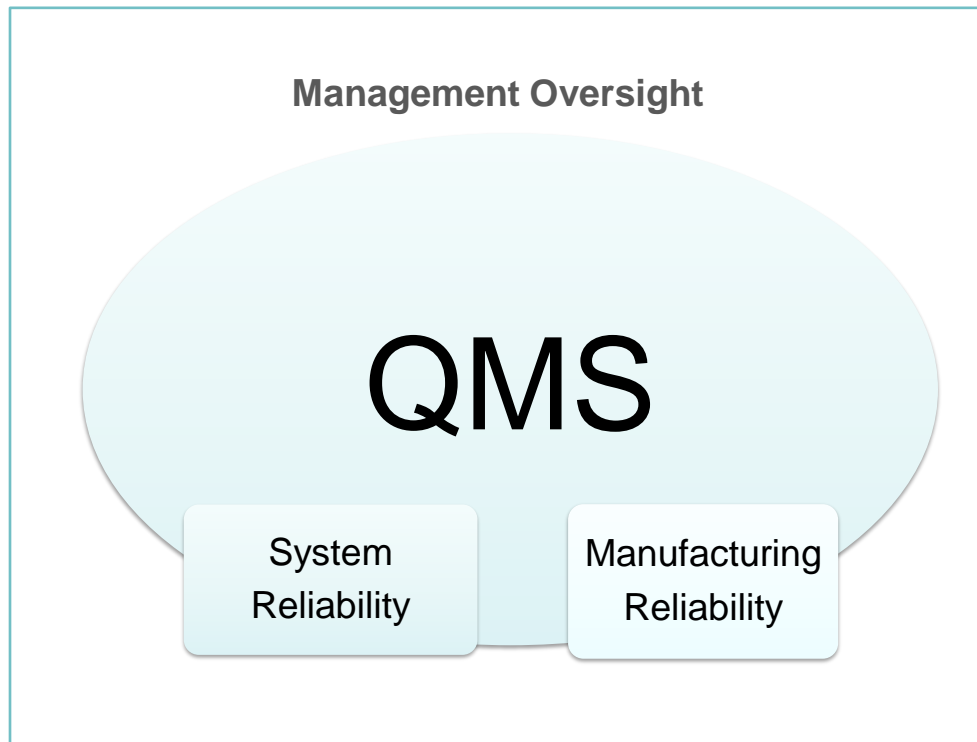
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Effective Quality Management Systems

An effective QMS (“quality system”) establishes and maintains a state of control throughout the product life cycle via systems that vigilantly oversee process performance and product quality.



Agenda Topics

- Change Control
- Quality by Design
- Quality Risk Management
- Continual Process Improvement
- Summary
- Exercise 1
- Exercise 2



Change Control

Change Control focuses on managing change to prevent unintended consequences. The CGMP regulations provide for Change Control primarily through the assigned responsibilities of the QU. Certain major manufacturing changes (e.g., changes that alter specifications, a critical product attribute, or bioavailability) require regulatory filings and prior regulatory approval.

Source: Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations

Why is this Important?

Documenting processes, associated controls, and changes to these processes will help ensure that sources of variability are identified.

Key Considerations for Change Control as Outlined in CGMP Guidelines and ICH Q9 Include:

The process design and scientific knowledge of the product

The monitoring and evaluation of the specific elements that may be affected

The documentation of changes to an established process/ procedure

The impact of the changes on the final product and patient safety

The effect of changes to the facility, equipment, material, manufacturing process, or technical transfers on product quality

The knowledge and information accumulated in pharmaceutical development and during manufacturing

The following questions should be asked and answered to help implement Change Control.

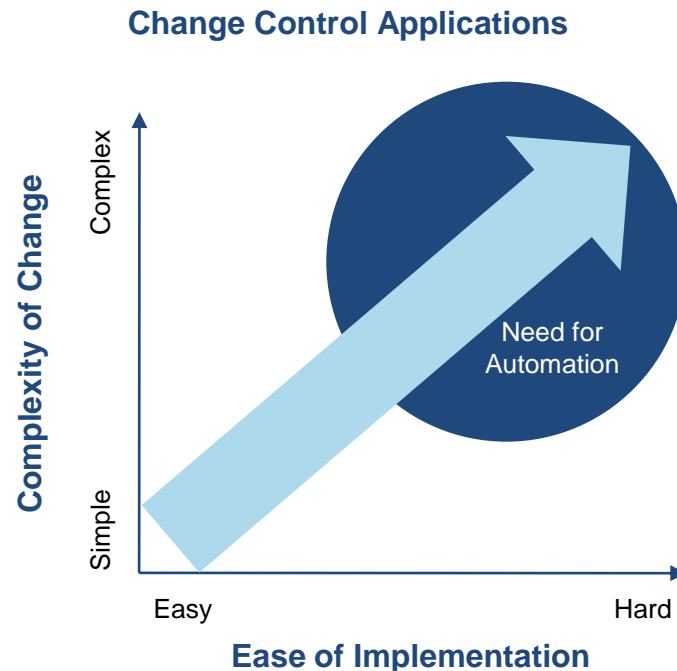
- What documents will be affected by this change?
- Will this change affect multiple sites?
- Which processes, facilities, and equipment will this change apply to?
- Will there be any validation requirements in order to implement this change?
- Will this change impact product quality/ patient safety?
- Will this change have any regulatory impact?
- Will this change affect suppliers?
- What training will need to be provided in order to implement this change?

When making a change to improve compliance, it is important to ensure it is appropriately implemented.

Considering the questions previously discussed, a Change Control Matrix can be used to identify the complexity and ease of implementation.

The four levels of Change Control complexity include:

- Level 1:** Basic Changes,
- Level 2:** Straightforward Changes,
- Level 3:** Complex Changes, and
- Level 4:** Integrated Complex Changes.



Change Control Summary

- Change Control provides a systematic approach to implementing change within an organization.
- All key elements of organizations must be considered, including (but not limited to):
 - Documents,
 - Facilities and Equipment, and
 - Employees.
- Changes vary based on complexity and ease of implementation, which must be understood to successfully implement change.

How QbD and QRM Relate

Before transitioning into QbD and QRM, let's look at how the two interact.

- QbD and QRM are two key processes for an effective QMS.
- Together, they are utilized to establish the most effective and efficient practices within an organization.
- They complement each other by ensuring that quality is kept in mind for both the design and improvement of processes.

Quality by Design

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and QRM.

Source: FDA Guidance for Industry Q8(R2) Pharmaceutical Development

Why is this Important?

QbD ensures a safe and effective drug supply, while also significantly improving the quality of manufacturing and performance. It ensures that the root causes of manufacturing problems are satisfactorily addressed and corrected, makes it easier to perform risk mitigation actions and subsequently avoid rejection of batches, and ensures greater batch to batch consistency.

Implementing QbD

Key steps for implementing QbD include:

- **Step 1:** Design a robust product formulation,
- **Step 2:** Design a robust manufacturing process,
- **Step 3:** Establish relevant product specifications, and
- **Step 4:** Continually evaluate for optimization.

Why is this Important?

The implementation of a robust QbD program reduces product variability and defects, as well as enhances manufacturing efficiencies.

Quality Risk Management

A systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the product lifecycle.

Source: FDA Guidance for Industry Q9 Quality Risk Management

Why is this Important?

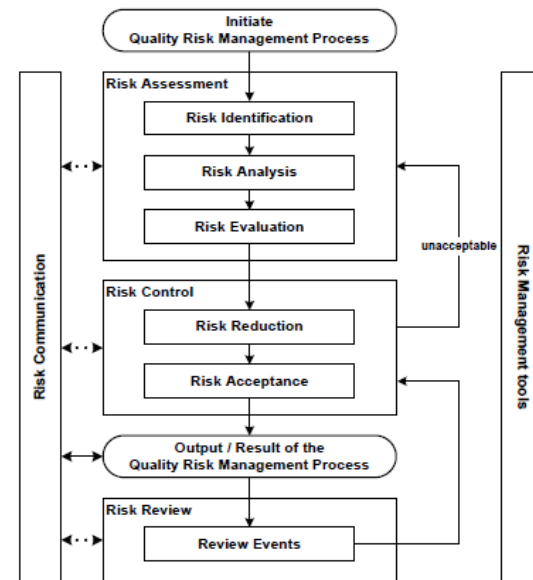
QRM increases product and process knowledge, which translates into greater control of product and process variability, and a lower residual risk to patients.

Implementing QRM

Key steps for implementing QRM include:

- **Step 1:** Plan must be reviewed and approved by an outsourcing facility's functional departments, such as Quality Management, Facility, Equipment and Utilities, Product, Laboratory, and Raw Materials,
- **Step 2:** Employees must be trained,
- **Step 3:** Plan must be documented accurately, and
- **Step 4:** Plan must be continually revised.

Risk assessment should occur early in the lifecycle, be controlled appropriately, and be communicated effectively.



See the figure in ICH Q9 [here](#).

QbD and QRM Summary

- QbD and QRM are processes that enable organizations to establish and maintain best practices for a positive QMS and Quality Culture.
- Effective implementation of each will allow for safe and efficient procedures.
- QbD and QRM ensure existing and potential risks are recognized and accounted for.
- QbD and QRM allow for Continual Process Improvement, which we will now discuss.

Continual Process Improvement

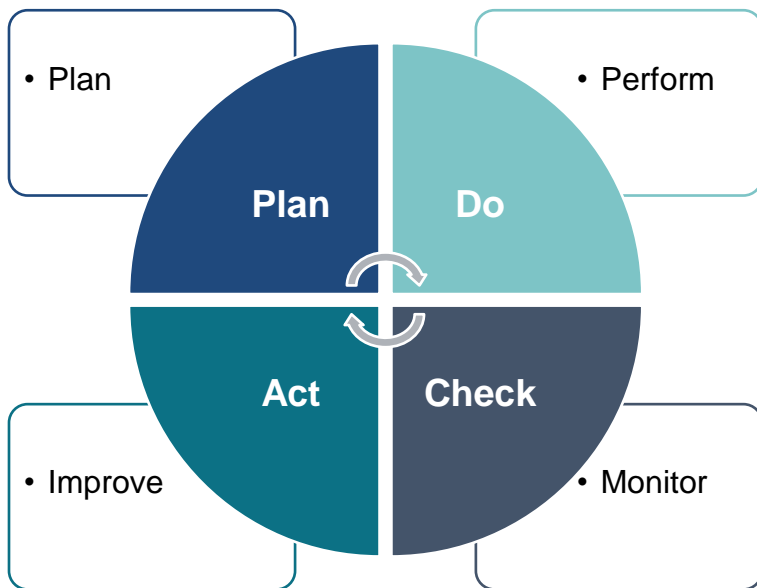
Ongoing activities to evaluate and positively change products, processes, and the quality system to increase effectiveness.

Source: Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations

Why is this Important?

It improves your compliance to regulations by ensuring your processes are capable of continually ensuring the manufactured product meets the regulatory requirements for identity, quality, purity, and safety.

Plan, Do, Check, Act



The PDCA cycle is an intentionally cyclical planning tool; and is most useful for continuous improvement when repeated often.

A few instances when the PDCA cycle is helpful include:

- Launching a project,
- Creating or revamping a process, product, or service,
- Defining repetitive processes, and
- Implementing any change.

Applying PDCA to 503B Examples

Example

Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas.



Application

- **Plan:** Map your facility.
- **Do:** Write a procedure, train, and collect samples.
- **Check:** Review results to determine if further changes are necessary.
- **Act:** Resample or implement those sample sites.

Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions.



- **Plan:** Determine your cleaning process.
- **Do:** Write a procedure and train.
- **Check:** Based on environmental data, determine if cleaning is effective. Are bacterial hits eliminated?
- **Act:** Enact changes to improve cleaning processes.

PDCA Summary

- Processes and procedures must be continuously monitored and improved to ensure quality is achieved and maintained.
- Continual Process Improvement is performed through the collection, interpretation, and evaluation of data.
- The PDCA cycle is a tool that can be used to implement change and continuously improve processes.

QMS Processes | Summary



- While their impact on organizations is separate, the following processes work together to establish QMS:
 - Change Control,
 - QbD and QRM, and
 - Continual Process Improvement (PDCA).
- Change Control establishes best practices for implementing changes within organizations.
- QbD and QRM ensure organizations are driving Continual Process Improvement and identifying risks associated with their operations.
- Continual Process Improvement ensures that organizations are maintaining a positive QMS.

Exercise 1

OBSERVATION 4

Employees are not given training in the particular operations they perform as part of their function, current good manufacturing practices and written procedures required by current good manufacturing practice regulations.

Specifically,

A.

Quality Control technician performing the sterility testing and the endotoxin testing for finished drug products has no documented training for conducting the QC sterility and endotoxin tests or general current good manufacturing practice training or current good documentation practice training.

B.

Process Engineer performing the labeling and the visual inspection on the visual inspection machine machine has no documented training of reading procedures.

C.

Quality Systems Manager training file contained no documentation for reading of the firm's SOP's.

Questions

What systems failed?

How would you respond to this scenario?

Exercise 2

- FDA investigators noted that **drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions**, whereby they may have become contaminated with filth or rendered injurious to health, **causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA.**
- The violations include, for example:
- **Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination** of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes. (21 CFR 211.113(b))
- **Your firm does not have**, for each batch of drug product purporting to be sterile and/or pyrogen-free, **appropriate laboratory determination of satisfactory conformance to final specifications for the drug product.** (21 CFR 211.167(a))
- **Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates.** (21 CFR 211.166(a))

Questions

What systems failed?

How would you respond to this scenario?

THANK
YOU

A 3D rendered graphic of the words "THANK YOU". The word "THANK" is positioned above "YOU" and is rendered in a light gray, blocky, sans-serif font. The word "YOU" is rendered in a vibrant red, blocky, sans-serif font. Both words have a slight shadow and are reflected on a glossy white surface below them. The background is a plain, bright white.