
FDA Failure Investigations and Quality Systems

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What is Quality?

- All pharmaceutical products must establish identity, strength, purity and other quality characteristics
- This assures the required levels of effectiveness and safety
- Achieving quality means achieving the desired characteristics for the product

What is Quality?

- **Quality** is also defined as measure of a product's or service's ability to satisfy the customer's stated or implied needs
- **Quality System** is the formalized business practices that define management responsibilities for organizational structure, processes, procedures, and resources needed to fulfill product service requirements, customer satisfaction and continual improvement

What is Quality?

- **Quality Unit** is a group organized within an organization to promote quality in practice
- **Quality unit** is required under CGMP §211.22
- Industry practice generally divides the **Quality Unit** into **Quality Control** and **Quality Assurance**
- **QC** involves assessing the suitability of incoming components, containers, closures, labeling, in-process materials, and finished products. Also evaluating the performance of the manufacturing process to ensure adherence to proper specifications and limits. In addition, to determining the acceptability of each batch for release.

What is Quality?

- **QA** reviews and approves all procedures related to production and maintenance
- **QA** reviews associated records
- **QA** audits and performs trend analysis
- **QA** evaluates trend analysis

What is Quality?

- The CGMP regulations specifically assign the **QU** the authority to create, monitor, and implement a quality system.
- **QU** should not take on responsibilities of other units of a manufacturer's organization such as responsibilities handled by manufacturing personnel, engineers and developmental scientists.

What is Quality?

- CGMP assigned responsibilities of the QU also consistent with a modern quality system approaches under **§211.22** are:
- Ensuring controls are implemented and completed during operations
- Ensuring developed procedures and specs are appropriate and followed including those used by a firm under contract to the manufacturer.
- Approving or rejecting incoming materials, in-process materials and drug products.

What is Quality?

- Reviewing production records and investigating any unexplained discrepancies.
- Under a quality system it is expected that the product and process development units, manufacturing units and QU remain independent.

What is Quality by Design?

- **Quality by design** -designing and developing a product and associated manufacturing process used during development to ensure that the product consistently attains predefined quality at the end of the manufacturing process.
- **Quality by design** works in conjunction with **quality system** to transfer product knowledge from development to commercial manufacturing.
- Aids in post-development changes and optimization.

What is Quality by Design?

Overall Pharmaceutical Development -QbD

- Systematic, relating mechanistic understanding to input product attributes, process parameters, and critical process parameters.
- Multivariate experiments to understanding product and process
- Design space

What is Quality by Design?

Quality by Design is knowing your Manufacturing Process

- Knowledge of design space; linkage between process inputs and critical quality attributes can be described in design space.
- Adjustable within the design space
- No matter how a design space is developed it is expected that operation within the design space will result in a product meeting defined quality attributes
- CQA are properties that impart desired quality, safety, and efficacy. Examples of CQA are: content uniformity, assay, stability of API, purity, micro, chemical stability.

What is Quality by Design?

Quality by Design is Lifecycle Management

- Preventive Action
- Continual improvement facilitated.

CGMP 21CFR 211

REQUIREMENTS FOR INVESTIGATIONS

Quality System

QU quality assurance

Review / Investigate/ Looping the Regulations Together

§211.22 (a) Responsibilities of quality control unit

§211.100 (a-b) Written procedures; deviations

§211.180 General requirements records reports

§211.192 Production record review

§211.198 (a) Complaint files

§211.115 Reprocessing.

CGMP 21CFR 211

REQUIREMENTS FOR INVESTIGATIONS

- Under **§211.22** the quality unit is required to review production records and investigate any unexplained discrepancies.
- In addition, under **§211.22** rejecting incoming materials, in-process materials and drug products. If rejected must conduct an investigation.
- Under **§211.22 (a)** QU is responsible for approving or rejecting products services provided under **§211.22 (a)**

CGMP 21CFR 211

REQUIREMENTS FOR INVESTIGATIONS

- Under **§211.192** a key component of a Quality System is handling nonconformities, and or deviations.
- In order to meet **§211.192** the investigation's
- conclusions and follow-up must be documented.
- Meeting **§ 211.192** also requires manufactures to set critical product attributes; specified control parameters and strength as required.
- The accurate measurement of the process and product attributes is also required to meet **§211.192**.

CGMP 21CFR 211

REQUIREMENTS FOR INVESTIGATIONS

- Know that discrepancies can be detected at any stage of the process or during quality control activities.
- Know that not all discrepancies result in product defects however it is important to document and handle them appropriately for inspections.
- Discrepancy investigations are critical when the discrepancy is found that it affects product quality and can lead to significant 483 items if not handled appropriately or completely.

CGMP 21CFR 211

REQUIREMENTS FOR INVESTIGATIONS

- In a quality system and to meet the CGMPs it is important to have SOPs that define who is responsible for halting and resuming operations regarding non-conformities.
- SOPs are also required defining who is responsible for investigating discrepancies and responsible parties involved in taking remedial actions.
- Under the CGMP and Quality Systems if the product or process does not meet the requirements qualified individuals must identify and segregate the product so that it is not distributed to the customer.

CGMP 21CFR 211

REQUIREMENTS FOR INVESTIGATIONS

What is remedial actions; examples:

- Correct the non-conformity if possible and within CGMP and applications
- With proper authorization allow the product to proceed with justification of the conclusions regarding the problems impact.
- Reject the product

CGMP 21CFR 211

REQUIREMENTS FOR INVESTIGATIONS

- Under **§ 211.115** process should be re-examined for conformance and assessed for significance of the non-conformance.
- If the non-conformance is significant (assay, purity) based on the process control, process efficiency, product quality, safety , efficacy and product availability remember to evaluate and document how to prevent the recurrence.
- If a product has not met its requirements and been released the product can be recalled. Customer complaints must be reviewed and then investigated per **§211.198**.

FDA Inspections-Investigations

Quality Systems

Production Systems

- **Quality Systems** required to be covered in every inspection whether abbreviated or comprehensive
- **Production Systems** is almost always also chosen by Drug Investigators

FDA Inspections -Investigations

Quality Systems

Production Systems

Quality Systems Key Items Covered

- Product reviews batches reviewed for each product, trends identified (investigations)
- Complaint reviews (quality and medical)
- Reprocess rework

FDA Inspections -Investigations

Quality Systems

Production Systems

Quality Systems Key Items Covered

- Failures
- Rejects
- Corrective actions, preventive actions

FDA Inspections-Investigations
Quality Systems
Production Systems

Production Systems Key Items Covered

- Justification and consistency of in-process specifications and drug product final specifications

- Master Production and control records

FDA Inspections-Investigations
Quality Systems
Production Systems

Production Systems Key Items Covered

- Batch production and control records
- Documented investigations into unexplained discrepancies

FDA Inspections-Investigations

Quality Systems

Production Systems

Inspection findings that demonstrate that a firm is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative and or judicial actions.

Quality System is out of control if there is a pattern of failure to conduct investigations and resolve discrepancies, failures, deviations , and complaints.

Production System is out of control if there is a pattern of failure to document investigations of deviations.

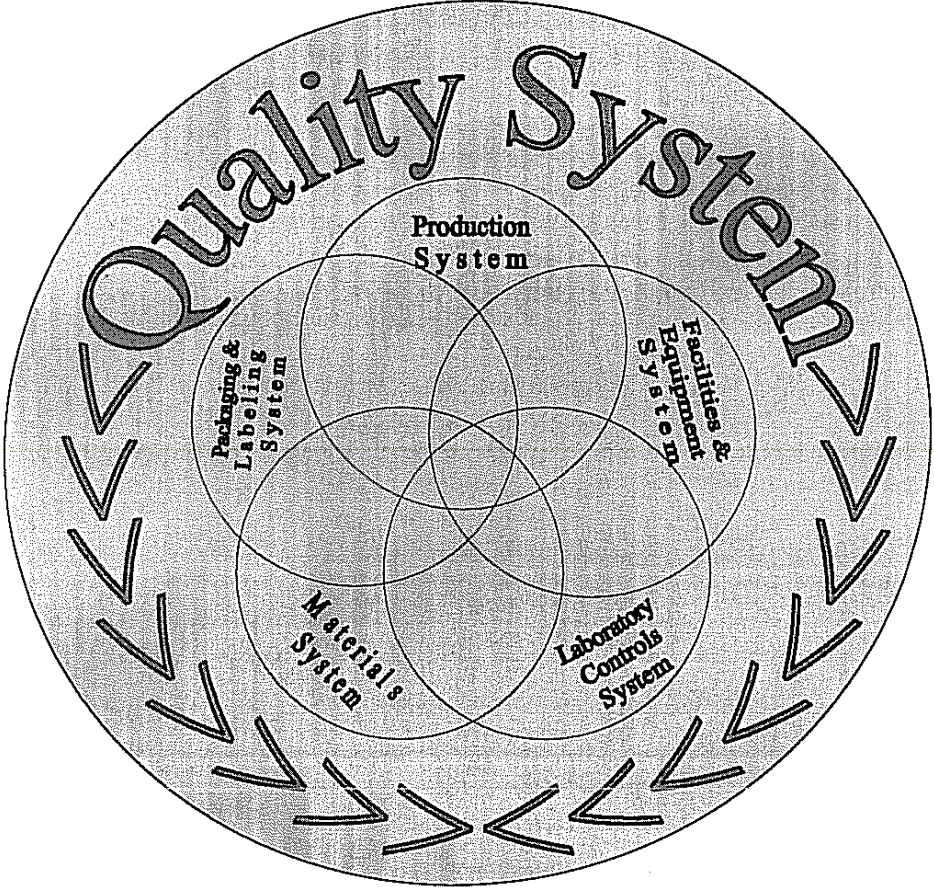
Laboratory System is out of control if there is a failure to document investigations of deviations.

FDA Inspections-Investigations

Quality Systems

Production Systems (one system fails all fails)

control.



CGMP Requirements for APR Trending Investigations

§ 211.180 (e)

- APR provide valuable information about products
- APR are required under **§ 211.180 (e)**
- Trending of complaints investigations
- Review of a representative number of batches.

CGMP Requirements for APR Trending Investigations

- Review of recalls and associated investigations
- Review of returns and associated investigations
- Review of all investigations required by
§ 211.192

Key CGMP Concepts

Manufacturing Investigations

Manufacturing Investigations

Part 211.100 Written Procedures, Deviations- providing written procedures for production and process control designed to assure that the drug products have the identity, strength, quality and purity they purport to have.

Part 211.192 Production Record Review any unexplained discrepancy or the failure of its batch or any of the components to meet predefined specifications.

Key CGMP Concepts

Manufacturing Investigations

- Also any other events that can possibly affect product identity, strength, quality, purity, or not following procedures should be investigated and documented. Also quality issues with components, raw materials, bulk received from suppliers should also be investigated.
- Investigations/deviation reports should have a time frame for completion. Usually within 30 calendar days.
- Responsibility crosses groups in an organization. For instance many investigations require the expertise of quality assurance, quality control, production, suppliers, engineering, and technology.
- Companies should have available for review extremely detailed procedures establishing steps that should be followed when documenting deviations.

Key CGMP Concepts

Manufacturing Investigations

Typical reasons for deviation reports and investigations.

- Deviations from manufacturing or packaging procedures
- Product mix up
- Wrong batch numbers
- Not meeting specifications
- Equipment malfunctions not meeting calibration schedules
- Out of range for yields
- Operating out of the set limits for a piece of equipment
- No training/ employee errors

Key CGMP Concepts

Manufacturing Investigations

Minimum information observed in a general deviation report or investigation report:

1. Heading/ introduction- Explaining the dates, batch numbers, SOP used. Materials effected.
2. Description of the event- Must be clear and concise.
3. Description of the investigation- Officials involved; QU involved; what was done to investigate the cause of the deviation; document all information that lead to a root cause or possible root cause; record all reasons for not following approved SOPs, must document thoroughly the potential impact on the batch or batches produced prior to the effected batch.

Key CGMP Concepts

Manufacturing Investigations

4. Conclusions- Officials involved document a resolution for the deviation and address all products that may be effected. Root cause is often discussed in this section.
5. Actions taken by the company- Does it make sense? Is the firm going conduct additional testing; additional maintenance conducted or equipment replacement needed; What is the rational for actions taken. Will it protect future batches from being affected.
6. Corrective Actions-requirements from firm's officials for corrective actions which can prevent noncompliance from occurring again. Should include timelines for completion.

Key CGMP Concepts

Manufacturing Investigations

- 7. Disposition- review by the quality team required of the materials that were or have a risk of being affected by the deviation.
- 8. Notification to the file- issued by quality indicating that the corrective actions have been completed.

Key CGMP Concepts

Manufacturing Investigations

Quarterly Reviews

Companies keep deviations in their data systems so they can be trended and reviewed quarterly and during FDA inspections.

- Data from the deviations are compiled and reviewed quarterly in deviation summary reports.
- Quality Assurance must review the deviation summary reports to determine a root cause and if there are any identified trends.
- If Quality Assurance identifies trends a deeper investigation should be conducted to determine appropriate corrective actions. Noted also in the APR.

Key CGMP Concepts

Laboratory Investigations

Lab investigations are conducted when there are questionable results. OOS

1. Companies should conduct a review to identify a lab error or need for full investigation.

2. Items that should be evaluated:

- data-lab note books

- methods

- calculations

- equipment

- sample integrity

- reagents, standards used in analysis

- training

3. Usually results in the following:

- correctable lab error-further investigation not needed. Error fixed and corrected results used (example wrong calculations).

- non-correctable lab errors- invalidate results and testing repeated. Investigation concluded.

- no lab error detected- Full Investigation-Quality Review to determine what to do with the batch; Manufacturing Investigation; Retesting performed and additional confirmation testing performed.

Key CGMP Concepts

Laboratory Investigations

Common Reasons for Lab Investigations:

Employee: SOP not followed; stability samples not pulled at right time; misreported data; lack of training; analytical errors; calculation error.

Facility: Lab contamination; no quality management; power failures

Methods: Unclear written methods; Method limitations; wrong methods used; outdated methods used.

Equipment: calibration failure; calibration frequency inadequate; old equipment; wrong equipment used for testing.

CAPA well known CGMP Concept

Corrective Action

§ 211.22 (a) Responsibilities of quality control unit

§ 211.192 Production record review

Preventive Action

Falls under a firm's CAPA program

CAPA well known CGMP Concept

What is CAPA

CAPA is a well known CGMP regulatory concept focusing on investigating, understanding and correcting discrepancies while attempting to prevent their recurrence.

CAPA tracks and trends quality events

Identifies true root causes

Tracks corrective actions to assure they have been implemented.

Measures the effectiveness of corrective preventive actions.

Prevents future non-conformances.

CAPA well known CGMP Concept

CAPA

- Remedial corrections of an identified problems
- Root cause analysis with corrective action to help understand cause of the deviation to prevent recurrence of the problem.
- Preventive action to avert recurrence of the problem.

Key CGMP Concepts

Change Control

- Change Control- a well known CGMP concept geared towards managing change safely.
- Change Control- should be managed by quality control unit with assigned responsibilities.
- Major changes that alter specifications, a critical product attribute or bioavailability requires regulatory filing and approval.

Key CGMP Concepts

Change Control

- Change Control Activities-require authorization to make changes.
- Usually involves Quality Assurance, Manufacturing, Packaging, Process Technology and Engineering.
- During inspections Change Control documents such as master documents which are circulated through specific departments for approval and review are evaluated.
- Companies often forget to train individuals in process changes or implement changes before they go through their change control process and approval process. This leads to FDA 483 observations for unapproved changes and lack of training.

Robust Quality System Why It Is Important

Robust Quality System = Less FDA 483

Very Popular FDA 483 Issued During Inspections

- § 211.22(d) Responsibilities of quality control unit
- § 211.100(b) Written procedures; deviations
- § 211.110(a) Sampling and testing of in-process materials and drug products.

Very Popular FDA 483 Issued During Inspections

- § 211.160(b) General requirements Lab
- § 211.100(a) Written procedures; deviations
- § 211.192 *****Production record review;
Investigations

Very Popular FDA 483 Issued During Inspections

- § 211.165(a) Testing and release for distribution
- § 211.188 Batch production and control records
- § 211.25(a) Personnel qualifications
- § 211.67(b) Equipment cleaning and maintenance

Q & A

- Questions and Answers