

COMPLAINTS – INVESTIGATION & REVIEW



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Presentation Outline

- Overview of Complaints – Investigations - Review
 - Define GMP terms and regulations associated with complaints (21 CFR 211.198) and failure investigations (21 CFR 211.192).
 - Demonstrate how to apply GMP regulations associated with complaints and failure investigations when conducting an inspection.

“The views expressed in this presentation are my own and should not be construed as FDA’s views or policy”

Complaints

COMPLAINT FILES

21 CFR 211.198



Perspectives

- Industry
- Regulators



Source of Complaints

- MedWatch
 - Form FDA 3500 – voluntary reporting for health care professionals, consumers, and patients
 - Form FDA 3500B – voluntary reporting for consumers
 - Form FDA 3500A – Mandatory Reporting for INDs, manufacturers, distributors, importers, user facilities personnel.
- Letters (could be anonymous)
- E-mail (could be anonymous)
- Phone Calls (could be anonymous)
- Salesmen / Doctors / Pharmacists
- Returns
- Competitors
- Others...



211.198 - Complaint Files

Require Written Procedures including:

- Review by the quality control unit (QCU) of any complaint
- Evaluation of possible failure of a drug product to meet any of its specifications
- Determination whether the complaint represents a serious and unexpected adverse drug experience that is required to be reported to FDA

Complaint Files - 211.198

Written record of complaint must include:

- Name and strength of product
- Lot number
- Complainant information
- Nature of complaint
- Reply to complainant

Complaint Files - 211.198

- 211.198(b)(2): Written records must include:
 - Findings of the investigation
 - Follow-up to the investigation
- 211.198(b)(3): Where an investigation under 211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

Complaint Investigations

- 211.98 calls out 211.192
 - thorough
 - extend to other batches
 - extend to other drugs
- written record including conclusion and follow-up

Inspections

- Complaint Summaries / Trending
 - Databases / Spreadsheet
 - sorted by drug
 - sorted by lot
 - sorted by problem keyword
 - records must “be maintained so that data therein can be used for evaluating the quality standards of each drug.” [211.180 (e)]

Failures

- When **analytical** and **microbiology** results observed are outside the established specification due to...
 - Assay
 - Sterility
 - Dissolution
 - Active Ingredients – required testing

Failure Investigations

What is a Failure Investigation?

- Assessment of any **discrepancy** or **failure** of a drug product (or any of its components) to meet a specification.
- Questions to address:
 - Source / root cause
 - Other batches involved
 - Other drug products
 - Conclusions and actions to prevent recurrence

Other Names for “Failure Investigation”

- Out of specification (OOS) Report
- Incident Report
- Unusual Incident Report
- Quality Event
- Notice of Event
- Process Deviation
- Lab Investigation Report
- Informal Investigation
- Formal Investigation
- Stability failures
- Micro Investigation
- Hold Report
- Reject Report
- Non-Conforming Material Report

Typical Deviations

- Failure to follow procedures
- Failure to follow laboratory methods
- Failure due to equipment malfunction
- Failure to meet the acceptable quality limit (AQL)
- Failure to collect environmental samples
- Failure during the routine cleaning
- Failure to ...

21 CFR PART 211

CURRENT GOOD MANUFACTURING PRACTICE (cGMP) FOR FINISHED PHARMACEUTICALS

Referred to Investigations

- 211.192 Production Record Review
- 211.198 Complaint Files
- 211.22 (a) Responsibilities of the QCU
- 211.100 (b) Written procedures; deviations
- 211.160 (a) Laboratory Controls; general requirements
- 211.165 (e) Testing and release
- 211.170 (b) Reserve Samples
- 211.188 (12) Batch Production and Records

21 CFR 210.1 c-GMPs

(b) The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) FD & C Act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

211.22 - Responsibilities of Quality Control Unit

- (a) There shall be a quality control unit that shall have the responsibility and **authority to approve or reject** all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the **authority to review production** records to assure that no errors have occurred or, **if errors have occurred, that they have been fully investigated.**
- The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or **held under contract by another company.**

211.160 - Laboratory Controls

- The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit.
- Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

211.165 - Testing and release

- (a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release.
- (b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

211.165 - Testing and release

- (f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected.
Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

211.192 -Production Record Review

All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the QCU to determine compliance with all established, approved written procedures before a batch is released or distributed.

Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed.

The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

A written record of the investigation shall be made and shall include the conclusions and follow-up.

So what is required?

... when a batch (finished product, API) or any of its components (raw materials, packaging components) fail to meet the established specifications:

- a written record of the investigation
- thorough investigation,
- extend to other batches of the same drug product
- the conclusions and follow-up
- corrections and corrective actions

What would you expect to see?

- Clear and accurate written investigation document
- Full description of the detected failure
- Investigation completed in a **timely manner**
- Comprehensive (**Full**) Assessment - of the processes storing area, and testing
- Review of the documentation including raw data
- History of similar failures
- Impact assessment
- Implemented corrections and preventive actions

Purpose

- Identify the root cause, the source failure, and/or most probable root cause
- Review of Processes and Procedures
- Enhance Training
- Ensure that corrective and preventive actions are implemented to avoid recurrence

Standard Operating Procedures (SOPs)

- SOP's to handle plant deviations and investigations
- SOP's laboratory-failures
- Pre-defined standard procedure establishing the laboratory controls
- **Unique assessment** of the processes, potential changes, and specific conditions ...

What are you looking for?



Are you looking in the right place?
Are you documenting the right issues?
Are you arriving at the right solutions?

An Example

- You find that Lot 1234, of a sterile injectable drug, failed the sterility test. The micro lab confirmed the test failure. The lot was rejected and not distributed. The firm felt they did all they could do.

Question: Did the firm do all they could do?

Another Example

- You find a Deviation Report that says, on 8/8/13 a technician doing a monthly velocity test found that the blowers in the HEPA filter unit over aseptic fill line 4 had shut down. The HEPA filter units failed the velocity check. The vials filled on line 4 on 8/8/13 were destroyed. The firm installed an alarm system to alert an engineer if a blower shuts down.

QUESTION: Did the firm do all they could do?

Some Pertinent References

- 21 CFR 210 and 211
- FDA Guidance for Industry - Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production
- FDA Guidance for Industry - Process Validation: General Principles and Practices
- USP 37 / NF 32 General Notices, Test Results
- USP 37 / NF 32 Chapter <1010> Analytical data – Interpretation and treatment
- ICH Guidelines

Questions ????????????



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