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BATCH DISPOSITION

CRITICAL ASPECT ON REVIEWING INVESTIGATION OF
- DEVIATION
- OUT OF SPECIFICATION

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BATCH RECORD COMPONENT

Main :

- Batch Record
- Analytical Testing Record/CoA
- Related form/checklist
- Environmental Monitoring Result
- Certificate of Conformance

Ad Hoc :

- Deviation Report
- OOS Report
- Validation Report

BATCH RECORD COMPONENT

Deviation Report

- Critical
- Major
- Minor

OOS Report

- Confirmed Lab Error
- Not Confirmed Lab Error → Deviation initiation

Health Authority Expectation :

No batch release until deviation/OOS report completed and necessary CAPA implemented

REGULATION OVERVIEW
USFDA 211 CFR

. 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 quality control unit 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**.

REGULATION OVERVIEW

WHO – Batch Record Review

17.20

QC records should be reviewed as part of the approval process of batch release before transfer to the authorized person. Any **divergence or failure** of a batch to meet its specifications should be thoroughly **investigated.**

The investigation should, if necessary, **extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy**. A written record of the investigation should be made and should include the conclusion and follow-up action.

OUT OF SPECIFICATION
Principle

- **Do not test until pass**
- **Do no cherry pick data**
- **No average the OOS data**
- **Do not invalided result without justification**
- **Do not eliminate data**
- **Any retest/reinject, reweighing, remeasurement, resampling must be justified with scientific base rational**

Note : All data must meet Data Integrity Criteria

Attributable – Legible – Contemporaneous – Original - Accurate – Complete – Consistent - Enduring – Available

(ALCOA +)

OUT OF SPECIFICATION
Key Question

- **Integrity of Sample?**
- **Analyst well trained?**
- **Testing Method robustness?**
- **Method Validity?**
- **Equipment performance?**
- **Reagent preparation/mobile phase/solvent and its expiry date?**
- **Reference Standard Performance?**
- **Other sample tested at the same time?**
- **Isolated/Systemic?**
- **Is the parameter registered/internal specification**
- **Is the product already in FG or still intermediate?**

OUT OF SPECIFICATION
Key Question

- **Audit Trail Data**
- **Correctness on :**
  - Sample preparation
  - Sample weighing
  - Calculation
  - Adjustment volume
  - Injection volume

Do not :

- **Jump to conclusion**
- **Prejudice directly to production**
- **Clueless retest/reinject, reweighing, re-measurement**

OUT OF SPECIFICATION
Common Failure in OOS

- **Level of detail of Method Analysis**
  - Sample preparation
  - Shaking process
  - Extraction
  - Pipetting
  - Too many ambiguous instruction
- **Legal artist**
- **Equipment/consumable part performance**
- **Unknown trick and best practices**
- **Non Robust Method**
- **Sample treatment**
- **Analyst level of experience**
- **Fatigue**

OUT OF SPECIFICATION
Steps

- **Level 1 : Confirmed Lab Error → Re-measured → Completed**
- **Level 2 : Lab Error not confirmed → initiate deviation notice to start investigation beyond QC area**

Key Point :

- Any other batch(es) that possibly impacted
- Is it isolated/systemic

DEVIATION INVESTIGATION
Principle

- **Clear problem statement**
- **Logical flow chronologies**
- **Understand end to end process**
- **Link problem statement with high possible cause**
- **Collect the facts and supporting information**
  - Interview Operator
  - Batch record
  - Validation data
  - Literatures
- **Do not jump to conclusion**
- **No one man show investigator**

Note : All data must meet Data Integrity Criteria

Attributable – Legible – Contemporaneous – Original - Accurate – Complete – Consistent - Enduring – Available (ALCOA +)

DEVIATION INVESTIGATION
Key Question

- **What's the problem, what we have deviated**
- **Criticality of the occurrences**
- **Where and when it was happened and when it was detected and reported**
- **Is the questioned parameter registered specification/internal specification**
- **Is it the first time case or recurrence?**
- **How's the trend data from previous batch**
- **Why it is happen on this batch only not at the other batch?**
- **Is the operation the same? Well trained?**
- **Is all parameter the same (supplier/lot) with other good batch?**
- **Is all raw material/packaging material the same?**
- **Is the procedure clear, detail without ambiguous instruction?**

DEVIATION INVESTIGATION
Key Question

- **Any influence from environment?**
- **Any issue or note on incoming raw material/packaging material?**
- **Equipment performance?**
- **Impact of the occurrence to patient safety**
- **Is this impact to product validity status?**
- **Can the we allocate the good part vs the bad part?**
- **Can it be reprocessed?**
- **Should the occurrence be justified and escalated?**
- **Should we put on stability before release?**
- **Should we consult the issue with RA team?**

DEVIATION INVESTIGATION
Key Question

Do not :

- **Jump to conclusion**
- **Be solo investigator**
- **Prejudice directly to human error, material**
- **Find “nice” way on investigation rather than the “right” way**
- **Clueless on releasing/accepting/reprocessing the product**

DEVIATION INVESTIGATION
Common Failure

- **Incorrect problem statement**
- **Unrevealed fact/information/chronologies**
- **Reported not in timely manner**
- **Difficult to isolated and allocate the issue**
- **Finger pointing instead of collecting facts/information**
- **Hiding data/information**
- **Dominant managerial level**
- **Jump to conclusion too fast**
- **Incapable investigator**
- **Directed investigation scheme**
- **Supply demand**

DEVIATION INVESTIGATION
Common Failure

- **Love to please type investigation/quality personnel**
- **Ineffectiveness CAPA**
- **Focus purely on value not on sustainability nor patient safety**
- **Lack of risk assessment and justification**
- **Lack of good business ethic conduct**
- **Lack of Quality Culture**

ROLE SEGREGATION
Investigator – QA Reviewer/Approver – QA Batch Disposition

- **Investigator/Investigator Lead :**
  - Area owner → Not QA
  - QA must be as independent reviewer/approver

- **QA Investigation Reviewer vs QA Batch Disposition**
  - Ideally should be segregated
  - As compliment to each other
  - Strong personality
  - Different final review./approver could be defined based on deviation criticality

KEY POINT TO REVIEW INVESTIGATION REPORT

Event Description (Define)

Does it describe what happened (can someone outside organization understand it)

(How, When, Where, Who…..)

- **When and how was it discovered**
- **When did happen**
- **Where did it happen**
- **Who was involved, including roles**
- **When was Quality notified**
- **Does it describe the as-is-process (actual vs requirement)**

NOTE: Potential root cause(s) are NOT included in the description

KEY POINT TO REVIEW INVESTIGATION REPORT

Event Classification (Define)

Is there sufficient information to appropriately classify the deviation as Major or Minor

Preliminary classification documented

Agreed by Quality

Immediate Actions / Impact Analysis (Define)

1. **Is immediate action documented, clearly, completely and in detail, e.g., what was done to contain the situation (lot, equipment, area, process, materials)**

2. **Is justification provided if no immediate action taken, rationale provided**

3. **Are appropriate risk mitigating actions taken**
   - To product
   - To equipment, area

KEY POINT TO REVIEW INVESTIGATION REPORT

Trend Evaluation / Preliminary Impact Assessment (Measure)

1. **Is the impact to other batches / lots / products assessed and described completely including potential impact to other sites / divisions**
2. **Are raw materials / components / critical process parameters / equipment / similar products, systems, etc. assessed**
3. **Is the time period / criteria defined and justified**
4. **Is historical search criteria complete and data effectively used to inform current investigation**
5. **Does the historical search thoroughly review CAPAs from similar events to evaluate their effectiveness and influence proposed CAPAs (Frequency of occurrence / reoccurrence**

KEY POINT TO REVIEW INVESTIGATION REPORT

Root Cause Analysis (RCA) (Analyze)

1. **Is the root cause analysis thorough and well explained**
2. **Is the RCA performed using appropriate methodologies (tools), applied correctly and included as attachments**
3. **Are a suitable number of methodologies used based on the nature of / complexity of event**
4. **Are all possible root cause elements covered or only most probable root cause**
5. **Are the reasons potential root causes ruled out clearly explain**
6. **Are all *causal factors confirmed, no unexplained data indicating additional causal factors**
7. **Does the investigation follow logically from the root cause analysis**
8. **Is the root cause category logical and can it be explained and defended based on facts presented in the investigation (Investigation must include a logical explanation of root cause and be defendable)**

KEY POINT TO REVIEW INVESTIGATION REPORT

Investigation / Scope Assessment (Measure, Analyze)

1. **Is the scope of investigation set appropriately and well supported**
2. **Are deviation events assessed for potential impact to product, equipment and material within the scope of investigation**
3. **Does the investigation provide a logical conclusion supported by appropriate details including product disposition**
4. **Are all decisions made documented in the investigation**
5. **Is the investigation fully carried out; not stopped too soon**
6. **Has Quality verified that the preliminary classification is still accurate or justified any change required**
7. **Is the chronology included in investigation**

KEY POINT TO REVIEW INVESTIGATION REPORT

CAPA (Improve, Control)

1. **Is the link from *causal factor to root cause to CAPA clear**
2. **Is each root cause addressed by CAPAs, as appropriate, and logically justified; the solutions can be implemented**
3. **Are the CAPA timelines and responsibilities reviewed and agreed to**
4. **Are CAPAs measurable and have achievable due dates**
5. **Do CAPAs have justification for effectiveness checks or none required**
6. **Are CAPAs designed to address the systemic cause, and not just the symptom**

Material Disposition / Product Impact (Measure)

1. Is the product impact analysis thorough, well explained and logically justified

2. Is the impact on the process logically justified

3. Is a specific product / material disposition proposed that is supported by the investigation and scientific rationale based on the assigned root cause; are all lots considered

KEY POINT TO REVIEW INVESTIGATION REPORT

Material Disposition / Product Impact (Measure)

1. **Is the product impact analysis thorough, well explained and logically justified**
2. **Is the impact on the process logically justified**
3. **Is a specific product / material disposition proposed that is supported by the investigation and scientific rationale based on the assigned root cause; are all lots considered**

Timing / Extension Requests (Define, Measure)

1. **Is deviation Initiated according to SOP requirements**
2. **Is deviations closed according to SOP requirements**
3. **Are extension requests timely, justified, and contain all required information**
4. **Are extension requests approved by Quality prior to initial due date**

KEY POINT TO REVIEW INVESTIGATION REPORT

Writing Style / Formality

1. Absence of jargon (verbiage not easily understood by the reader)
2. Abbreviations explained
3. Sentence structure concise with no extraneous words, easily understood, use of active voice
4. Connection between ideas are clear
5. No inflammatory language
6. No mechanical errors (grammar, spelling, usage)
7. All referenced documents are attached
8. Report gives reader confidence the investigation was thorough; without statements that leave the reader with unanswered questions or open-ended possible root causes
9. All sections contain the necessary information and all information is in the appropriate section
10. Report is written in a logical flow (chronological, process flow, etc.) to ease reader understanding.

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DEVIATION INVESTIGATION
Key Point

- **If we could not understand our investigation report neither the external people (i.e auditor)**
- **If we do not understand our investigation report how could we release the batch?**


GRACIAS
THANK
YOU
ARIGATO
SHUKURIA
BOLZÍN
MERCI
BIYAN


TIME FOR QUESTIONS
12
1
2
3
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