Out of Specification (OOS) Investigations

Peter Cannon

GMP Inspector

HPRA GMP Information Day

4th & 5th May 2022

Radisson Blu Royal Hotel, Dublin

Agenda

- 1 – Regulatory Background
- 2 – Potential Consequences (What if ?)
- 3 – Work Process
- 4 – Examples of Deficiencies
- 5 – Takeaways

1. Regulatory Background

Eudralex Volume 4
Part I: Basic Requirements for Medicinal Products

- **Chapter 6 Quality Control**
  - On-going stability programme
    - *6.32 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with chapter 8 of the GMP Guide and in consultation with the relevant competent authorities.*
- **Annex 16 Section 1 Certification**
  - *1.7.16 All investigations pertaining to the batch being certified (including out of specification and out of trend investigations) have been completed to a sufficient level to support certification*

Eudralex Volume 4
Part II: Basic Requirements for Active Substances used as Starting Materials

- **6.6 Laboratory Control Records**
  - 6.61 Complete records should also be maintained for: ..... *and -Out-of-specification (OOS) investigations.*
- **6.7 Batch Production Record Review**
  - *6.72 All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.*
- **8.3 In-process Sampling and Controls**
  - *8.36 Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.*
- **11.1 General Controls**
  - *11.15 Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any re-sampling and/or retesting after OOS results should be performed according to a documented procedure.*

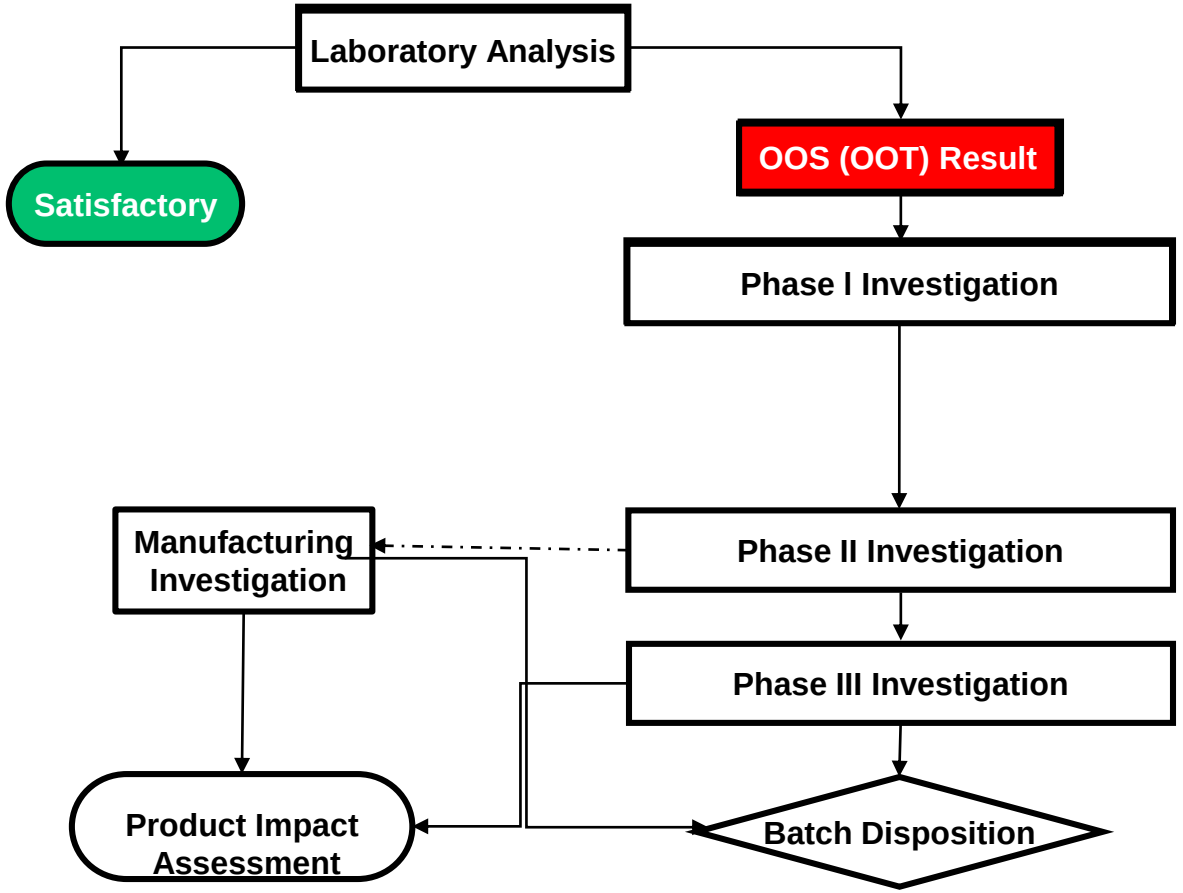
2. Potential Consequences to Mishandled OOS

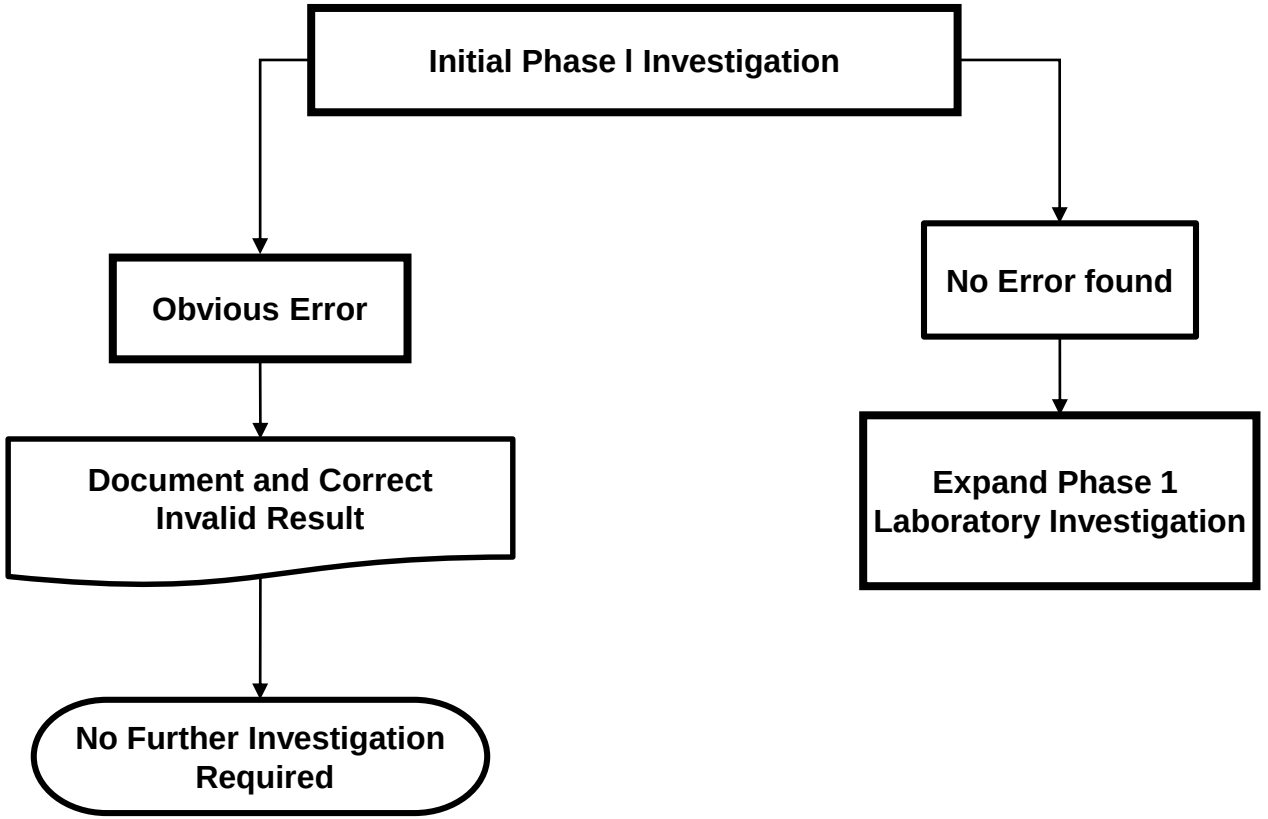
Serious Potential Consequences to Poorly Managed OOS's

- Patient harm
- Impact on stability programme
- Result in Quality Defect Reports
- Customer complaints
- Potential product recalls
- Major impact on schedule, more frequent Regulatory audits

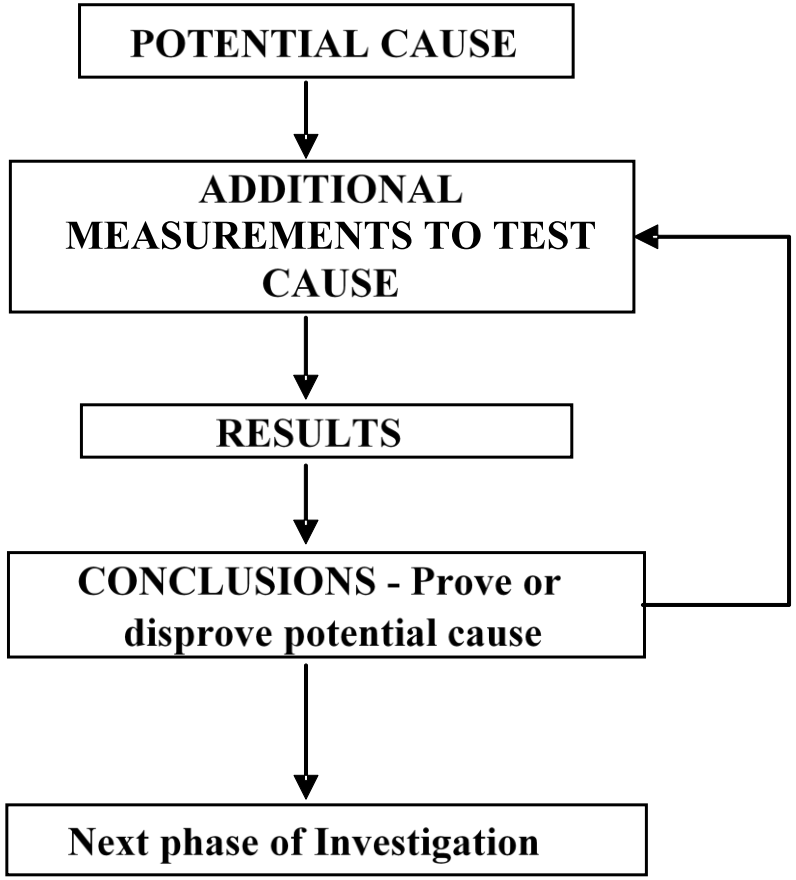
Lab is pivotal to early identification of issues

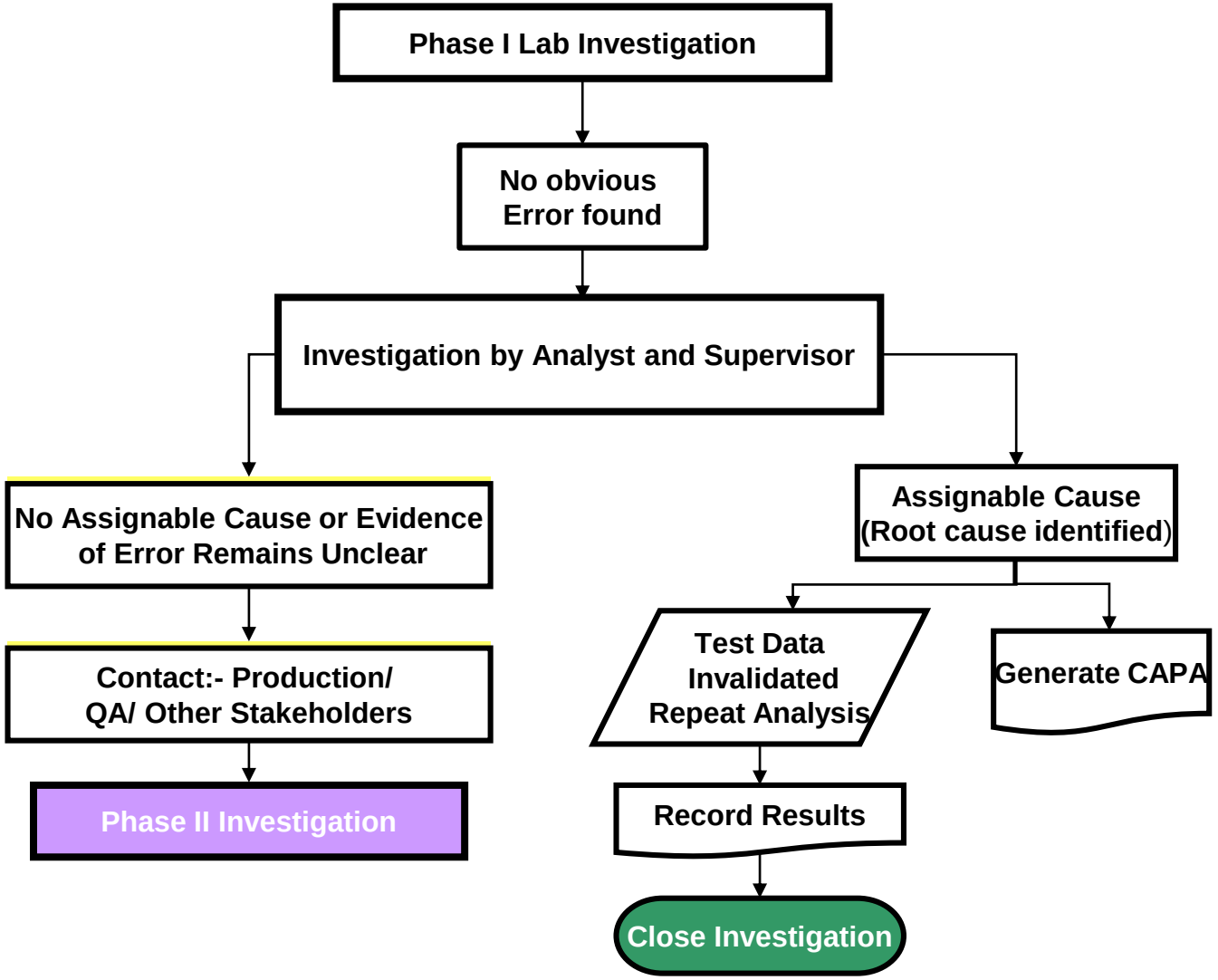
2. Work Process

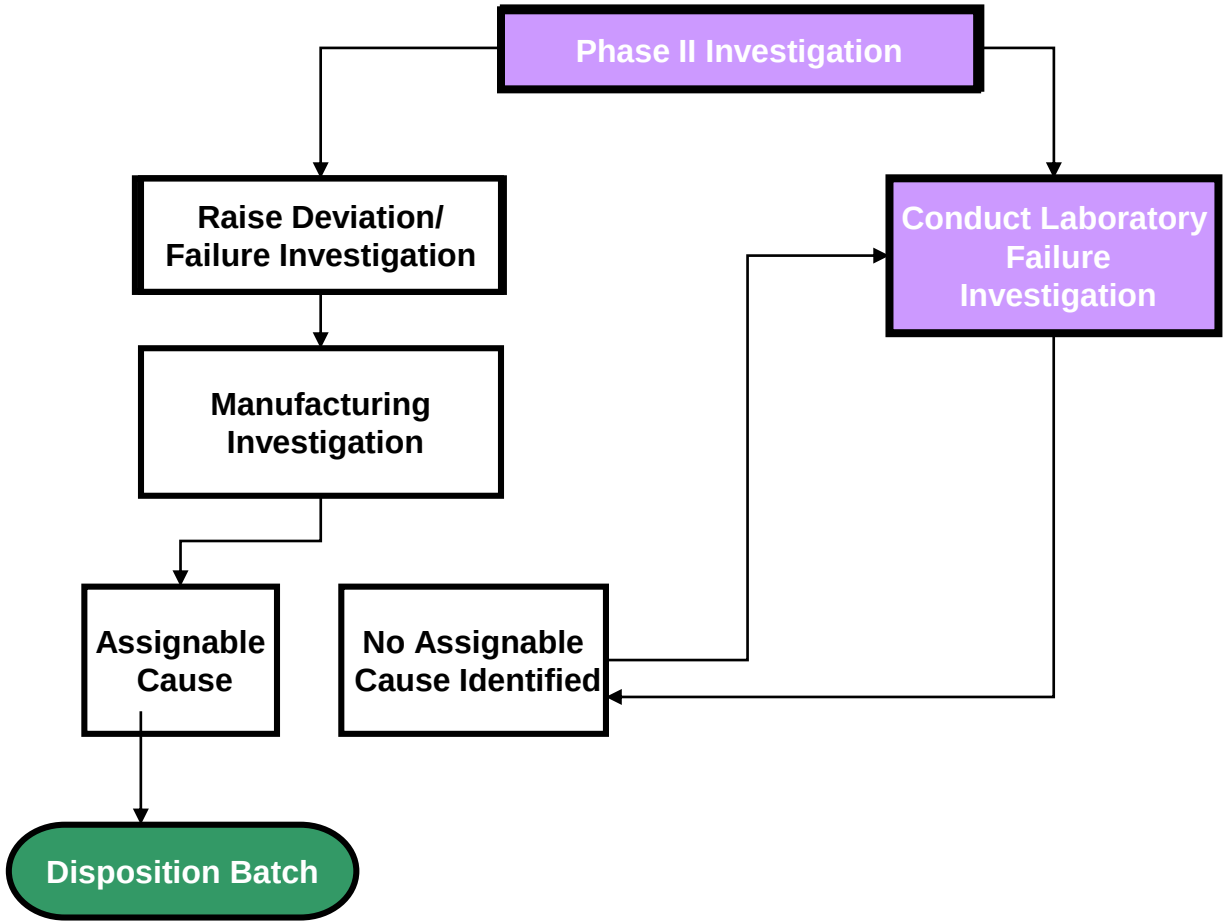

Laboratory Analysis
Satisfactory
OOS (OOT) Result
Phase I Investigation
Phase II Investigation
Manufacturing Investigation
Phase III Investigation
Product Impact Assessment
Batch Disposition

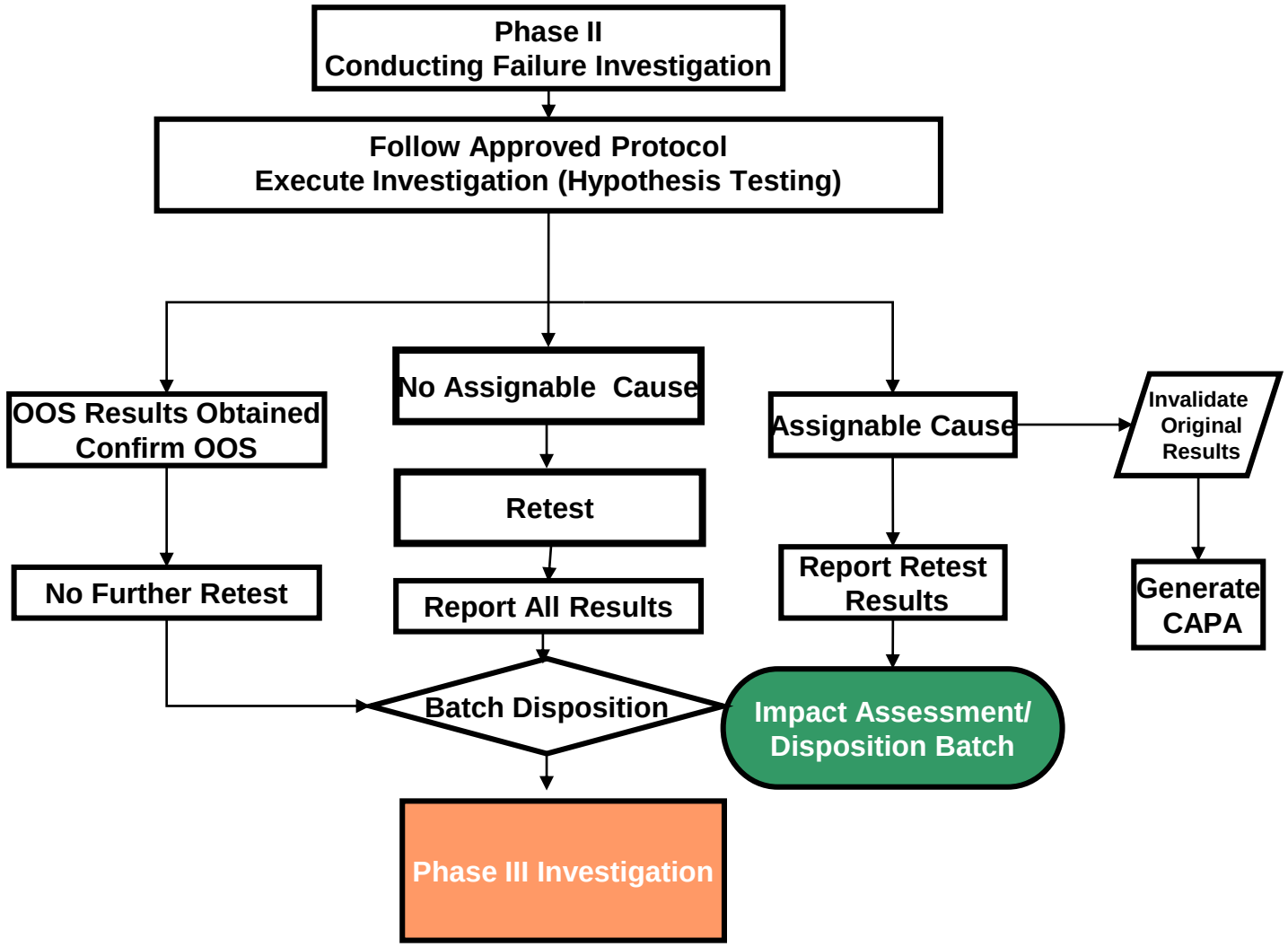

Initial Phase l Investigation
Obvious Error
No Error found
Document and Correct Invalid Result
Expand Phase 1 Laboratory Investigation
No Further Investigation Required

Investigational Measurements




Phase I Lab Investigation
No obvious Error found
Investigation by Analyst and Supervisor
No Assignable Cause or Evidence of Error Remains Unclear
Contact:- Production/ QA/ Other Stakeholders
Phase II Investigation
Assignable Cause (Root cause identified)
Test Data Invalidated Repeat Analysis
Generate CAPA
Record Results
Close Investigation


Phase II Investigation
Raise Deviation/ Failure Investigation
Manufacturing Investigation
Assignable Cause
No Assignable Cause Identified
Conduct Laboratory Failure Investigation
Disposition Batch


Phase II
Conducting Failure Investigation
Follow Approved Protocol
Execute Investigation (Hypothesis Testing)
OOS Results Obtained
Confirm OOS
No Assignable Cause
Assignable Cause
Invalidate
Original
Results
Retest
No Further Retest
Report All Results
Report Retest
Results
Generate
CAPA
Batch Disposition
Impact Assessment/
Disposition Batch
Phase III Investigation

Resampling for Retesting

- Should only be under exceptional circumstances, the original sample should be sufficiently large to permit additional testing in the event of an OOS.
  - If investigation concludes that the original sample was not representative of the batch or was compromised in some way.
  - If resampling is justified scientifically it should be performed by same qualified method that was used for the initial sample.
  - If the investigation concludes that the initial sampling method was deficient a new sampling method should be developed, qualified, documented and approved by Quality Mgt.

Resampling when justified must always be approved by Quality Mgt.

3. Recent Deficiencies

Deficiencies Relating to the OOS Procedure

Hypothesis Testing, the procedure

- Did not require *formulation of hypothesis for retesting* where no obvious lab assignable cause identified during the initial lab investigation.
- Did not *explicitly state Quality Management approval required* prior to proceeding to hypothesis testing.
- Did not clearly state that hypothesis testing/investigative testing was used *to identify* a potential lab root cause and *such test results could not be reported as the final result*.

Manufacturing Investigation

- Did not *clearly document at which stage a manufacturing investigation was initiated* and there was no assurance that such an investigation was completed prior to formal retesting.

Deficiencies Relating to the OOS Procedure

Retesting, the procedure

- Did not specifically state that retesting was *required to be documented and pre-approved by Quality Management*.
- Did not require *documentation of rationale for formal retesting* being carried out by a second analyst.
- Allowed for *averaging of retest results* but *did not explicitly state that all such results must be within specification*.

Deficiencies Relating to the OOS Procedure

Miscellaneous:

- *Reanalysis/retesting was performed in lieu of investigative testing* yet these results were averaged and reported in a number of cases reviewed.
- *Resampling did not require prior documented approval* by Quality Management.
- The procedure *did not specify a timeline for the completion* of the laboratory investigation.
- The *date of discovery was not recorded* on the OOS form and therefore it could not be verified that the record was raised in a timely manner.

Example Deficiency

Hypothesis Testing not documented and justified:

- Investigation was deficient as follows:

  Retesting as part of the secondary investigation included testing by a second analyst, re-preparation of standards due to suspected glassware contamination, change of mobile phase due to suspected contamination, change of column due to suspected column contamination and change of HPLC instrument.

  There was no documented evidence within the report that any of this retesting had been pre-approved.

Example Deficiency

Hypothesis Testing not supported by data and justified:

- With respect to OOS for individual impurity and total impurities the following was noted:
  - *The performance of re-testing as part of the Phase 1 investigation was not suitable or in line with the company's procedure as an obvious root cause had not been determined*.
  - The LIR concluded that the OOS was due to 'dirty glassware' however, *there was no evidence to support this conclusion and no CAPA had been raised to address this issue.*

- The investigation, ……relating to a low assay was deficient as follows:
  - The original OOS results were invalidated based on duplicate re-test results only and the *hypothesis that the HPLC column was the root cause was not supported by evidence* in that:
    - *No hypothesis testing had been performed* to demonstrate that the column was the source of the issue.
    - The *data from the reference batch, tested as part of the investigation conflicted with the hypothesis* that the column was the root cause for low assay result.

Example Deficiency

Investigative Test Results Reported

In a number of cases, where *in specification results were obtained during hypothesis testing*, these results *were used as the reportable result*. For example:

- Regarding the investigation …… relating to an OOS for Assay …… :
  - The hypothesis that the root cause of the OOS result was an instrument issue was not proven. *The hypothesis that the repeat analysis result was due to addition of excess material during weighing was not tested and proven* as part of the investigation.
  - An in-specification *result from a second repeat analysis under a different hypothesis*, (OOS result was due to a problem during extraction) *was used as the reportable result*.

Example Deficiency

Lack of Robust Impact Assessment

- The investigation of regarding product A Batch 1, which was OOS for low assay, was deficient in that:
  - The investigation indicated that the *OOS result was* valid and no root cause could be identified, however:
    - *No consideration was given to the potential impact on previous lots* of Product A released.
    - *No re-assessment* of the risk associated with a previous investigation *relating to an OOS for the same parameter* for a batch of product A *was performed in light of this OOS*.

Note: The batches in question had been manufactured consecutively.

Example Deficiency

Resampling not documented and justified:

- The investigation, LIR-A, relating to a higher than normal level of residual Solvent B in Product C included resampling and retesting of individual drum samples of Product C *without a documented rationale for resampling having been approved by Quality Management*.

- The investigation LIR–B, relating to an OOS moisture content on the composite sample of material D included resampling of all X individual drums of the batch.

  Individual drum samples were retested and two drums with high KF were removed from the batch. The batch was released based on testing of the composite of the remaining X-2 drums. The *resampling and retesting strategy had not been documented in a protocol approved by Quality Mgt and there was no documented justification for the deviation from the standard sampling and release process*.

Takeaways

- OOS Procedure in place and followed.
- Comprehensive investigation & CAPA follow up.
- All OOS results documented.
- Documentation to appropriate standard:
  - Easy to follow.
  - Logical flow.
  - Use of comprehensive checklists.
  - Protocols used for Hypothesis and any Additional Testing, justify everything.
- OOS results & investigations are reviewed at regular intervals:
  - Are identified issues isolated or recurring.
  - Are there trends.
  - Are issues investigated and closed in a timely manner.

Resources

- European Union:
  - Eudralex Volume 4
- United States:
  - FDA Guidance 2006: Investigating of out-of–specifications (OOS) test results for pharmaceutical production
  - United States v. Barr Laboratories, Inc., 812 F. Supp. 458 (D.N.J. 1993)
- MHRA Guidance:
  - Out of specification investigations
- WHO:
  - WHO guidance on testing of “suspect” falsified medicine

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Thank you