Template Provided By:

Cancer Imaging Program

National Cancer Institute

Standard Operating Procedure

GEN-Q015

Investigating Out of Specification QC Test Results

1. **Purpose:** FDA regulations require an investigation be conducted for any out of specification (OOS) test result to determine the root cause. The investigation should be timely, unbiased, well-documented, thorough, and scientifically defensible.

2. **Scope:** To describe the procedure for investigating out of specification (OOS) QC test results to be utilized at the sites manufacturing radiopharmaceuticals.

3. **Responsibilities:**
   The overall goal of the Out of Specification (OOS) investigation is to determine (1) the validity of the OOS result, and (2) the significance of the OOS result for the test product, other products that might be similarly affected, and the relevant production and testing processes.

   3.1. *Manufacturing Site(s)*: To follow this procedure as written and to ensure that all results, control information, and raw data are documented as specified in dedicated Quality Control Laboratory Notebooks and recorded on the appropriate testing, variance, and investigation forms.

   3.2. QC Analyst: To be aware of potential problems that could create out of specification (OOS) results during the testing process and utilize only those analytical instruments that meet established specifications and that are properly calibrated as per the manufacturer's recommendations. Certain analytical methods have system suitability requirements. If the reference standard responses indicate that the system is not functioning properly, all of the data collected during the suspect time period should be properly identified and invalidated. The analyst should not continue a test when an error has become obvious for example; a pipet tip falls off suggesting inaccurate measurement is likely. The cause should be

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identified and corrected. Before discarding test or standard preparations, check the data for compliance with specifications. If unexpected results are obtained and no obvious explanation exists, retain the preparations and notify the supervisor immediately, as an assessment of the accuracy of the results should be initiated in a timely manner.

3.3. QC Laboratory Supervisor: The supervisor should give an objective and timely assessment once the OOS has been identified, there should be no preconceived assumptions as to the cause. Data should be promptly assessed to ascertain if the results may be attributed to laboratory error, or if they are an indication of problems in the manufacturing process. An immediate assessment could include re-examination of the actual solutions, test units, and glassware used in the original measurements and preparations, allowing more credibility to be given to the laboratory error hypotheses. The assignment of a cause for OOS results will be greatly facilitated if the retained samples are examined promptly. It is important that each step in the investigation be fully documented. The supervisor should not only ascertain the reliability of the individual values in the overall quality assurance program, but the significance these OOS results represent as well. Supervisors should be especially alert to developing trends. Laboratory error should be relatively rare. When clear evidence of laboratory error exists, laboratory test results should be invalidated. When evidence remains unclear, a failure investigation should be conducted to determine what caused the unexpected results.

4. References

4.1 Guidance for Industry, Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production—September 1998 (CDER)

4.2 **GEN-M120,** "Documentation of Manufacturing Variances**"**

4.3 Gamerman GE, et al. Resolving Out-of-Specification Results, *Journal of cGMP Compliance*, p 45-51.

5. Forms

- **Form MVR-001**, "Manufacturing Variance Report Form"
- **Form IOS-001**, "Investigating Out of Specification (OOS) QC Test Results Form"
- **Form FQC-002**, "Final Product QC Testing" Form II

6. Policies

6.1 Product Batch rejection does not negate the need to perform a laboratory investigation. Even if a batch of product is rejected on the basis of an out of specification (OOS) result, the investigation is still necessary to determine if the result is associated with other batches of the same product.

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6.2 A complete written record of the investigation should be made including the conclusions of the investigation, follow-up, and any possible preventative measures that can be initiated.

6.3 The initial phase of the investigation should include a careful examination of the laboratory's data, prior to discarding the testing solutions, samples, etc. All hypotheses regarding laboratory error or instrument malfunctions may be tested using the same test solutions. If this initial assessment indicates that no laboratory errors were made, a complete failure investigation should follow.

6.4 Statistical treatments of data should not be used to invalidate a discrete chemical test result. Only after a full investigation has failed to reveal the cause of the OOS result, should a statistical analysis assessment of the probability of the OOS result as discordant be considered for providing perspective on the overall quality evaluation of the batch.

6.5 Records must be kept of complete data derived from **all tests** performed to ensure compliance with established specifications and standards.

6.6 If no laboratory or statistical errors are identified in the first test, then no scientific basis exists for invalidating the initial OOS results in favor of passing retest results. All test results, both passing and suspect, should be reported and considered in the final batch release decisions.

6.7 Retesting *should* ideally be conducted by an analyst other than the one who originally performed the analysis, if the site has sufficient personnel.

6.8 Refer to the specific QC Testing, Review, & Final Release SOP for the testing requirements of individual products.

7. Materials and Equipment

7.1 Refer to the specific testing SOP for the appropriate materials and equipment if a retest is to be performed.

8. OVERALL OOS ACTION AND DECISION OUTLINE

8.1 The first action of the analyst is to properly document the OOS result and alert the laboratory supervisor, so the laboratory supervisor can initiate the OOS investigation.

8.2 The next step is to identify the cause of the OOS result (e.g., test error or product deficiency).

- **8.2.1** Check Analytical/ QC Supervisor's Initial Assessment
- **8.2.2** Check Trend Historical Data
- **8.2.3** Check Batch record/ General Investigational Principles
- **8.2.4** Determine and Implement the Retest and Resample Plan

8.3 Make a Release/Reject decision and document it based on the completed retests and data analyzed during the OOS investigation.

8.4 Undertake corrective action as necessary. Additional process development and controls should be considered where process problems are indicated to prevent recurrence. The corrective action must be documented, and verified.

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9. PROCEDURES

9.1 QC SUPERVISOR'S INITIAL ASSESSMENT

9.1.1 Discuss the test method with the QC Analyst to verify his/her knowledge, compliance, and performance of the correct procedure.

9.1.2 Examine the raw data obtained in the analysis, including any chromatograms and/or spectra, and identify anomalous or suspect information.

9.1.3 Review the QC laboratory notebook and associated test forms for possible transcription, measurement, or calculation errors.

9.1.4 Confirm the performance, calibration, maintenance, and suitability checks of the analytical equipment. Ensure all operational features are functioning properly (e.g., settings, temperatures, cleanliness of cuvettes, and detector windows).

9.1.5 Determine/verify that appropriate reference standards, solvents, reagents, and solutions were used and that they all meet quality control specifications and are within their expiration dates.

9.1.6 Evaluate the standards for the test method to ensure that the test is performing as expected based on the method validation data.

9.1.7 Document all steps and data collected during this part of the assessment, and choose the appropriate choice in the table below based on your assessment.

9.1.8 Ask the analyst to proceed, as directed once the appropriate choice of **A, B, or C** has been determined from **Table 1**.

TABLE 1

Choice	If	Then
A	clear evidence of laboratory errors exist	the OOS investigation can be terminated. Record corrective actions and document OOS results as invalid. Initiate retesting as appropriate to provide release data. The retest results alone will be the basis of the final product release, although the initial OOS results must be reported in the batch record with an explanation, on Variance Report Form, **Form MVR-001**. Proceed to Step **9.3.**
B	Evidence Remains Unclear	Proceed to Step **9.2** and conduct a failure investigation to determine what caused the unexpected results.
C	Laboratory Error Is Identified	Proceed to step **9.2**, and determine the source of error. Take corrective actions to ensure that the error does not recur.

9.2 INVESTIGATING OOS TEST RESULTS

When the initial assessment determines that laboratory error **is not** the cause of the OOS result and the testing results appear to be accurate, conduct a full-scale failure investigation using the General Investigational Principles procedure below. The objective of this investigation is to identify the source of the OOS result.

9.2.1 General Investigational Principles

A failure investigation should consist of a timely, thorough, and well-documented written review that follows these general steps:

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9.2.1.1 The reason(s) for the investigation should be clearly defined.

9.2.1.2 The sequences in the manufacturing process that may have caused the problem should be summarized.

9.2.1.3 Results of the documentation review should be provided with the assignment of actual or probable cause.

9.2.1.4 A review should be made to determine if the problem has occurred previously.

9.2.1.5 Corrective actions taken should be described.

9.2.1.6 The general review should include a list of any other batches and/or products that could possibly be affected and any required corrective actions taken.

9.2.2 Laboratory Phase of an Investigation

If laboratory error was identified as the cause of the out of specification result then a retest must then be conducted, based on the results of the initial assessment of the QC Supervisor.

9.2.2.1 Retesting a Portion of the Original Sample: Part of the investigation may involve retesting a portion of the original sample. Retesting is appropriate for investigating instrument malfunctions or to identify a possible sample handling integrity problem, *i.e.*, suspected dilution error.

9.2.2.1.1 Obtain the QC Supervisor's Initial Investigation Assessment and subsequent Authorization to perform the retest on the original sample.

9.2.2.1.2 Document the retest on the **Form IOS-001**, "Investigating Out of Specification (OOS) QC Test Results Form."

9.2.2.1.3 Retest a portion of the original sample using the same quality control testing SOP. If the volume of the original sample is insufficient to allow for retest, obtain an additional sample volume from the final vial for retesting.

9.2.2.1.4 The retest results will substitute for the original test results although, the original test results should be retained, with an explanation well-documented on **Form IOS-001**. This should be initialed and dated by the involved persons on the **Form IOS-001**, "Investigating Out of Specification (OOS) QC Test Results Form," and include a discussion of the error and supervisory comments.

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9.3 CONCLUDING THE INVESTIGATION

To conclude the evaluation, the tests results should be evaluated and the overall quality evaluated to determine whether the lot should or should not be released.

9.3.1 Interpretation of Results: Release/Reject Decision

An out of specification test result does not automatically "fail" a batch of product. The OOS result should be thoroughly investigated and the findings of the investigations interpreted, including the retest results, for evaluating the fate of this batch regarding the final release or rejection decision.

9.3.1.1 If the investigation has revealed a cause, and the suspect test result is invalidated, then the result should not be used to evaluate the quality of the batch.

9.3.1.2 If the investigation indicates an OOS result is caused by a factor affecting the batch quality (*i.e.*, an OOS result is confirmed), the result should be used in evaluating the quality of the batch. A confirmed OOS result indicates that the batch does not meet the established specifications and should therefore be rejected.

9.3.1.3 If the investigation is inconclusive (1) it does not reveal a cause for the OOS test result and (2) does not confirm the OOS result, the OOS result should be retained in the record and given full consideration in the batch disposition decision.

9.3.1.4 The decision must be recorded on **Form IOS-001**, "Investigating Out of Specification (OOS) QC Test Results Form," and the final test result captured on the final QC test sheet, (Form FQC-001 or Form FQC-002).

9.3.2 Undertake Corrective Actions

9.3.2.1 If production or analytical error is shown, take corrective action to identify any other products or testing that might be affected.

9.3.2.2 Identify what actions are necessary to prevent future errors.

9.3.2.3 What additional process development and controls should be considered to prevent recurrence of this incidence if it was process related?

9.3.2.4 Document and verify the implementation of the corrective actions.

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