Frederick National Laboratory for Cancer Research, Frederick, MD

Biopharmaceutical Development Program

Standard Operating Procedure

Title: Managing Out-of-Specification, Out-of-Trend or Unexpected Test Results

SOP Number: 22004

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1.0 Purpose

This SOP provides a procedure to be followed for the management, investigation and review of Out-of-Specification (OOS), Out-of-Trend {OOT), or unexpected test results found as a result of analytical testing in cGMP environments.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted]

2.0 Scope

This SOP covers the handling of OOS/OOT results that may occur with laboratory testing of product (raw materials, in-process, finished product, and stability samples) during clinical or production operations conducted by either Biopharmaceutical Development Program (BDP), Process Analytic/Quality Control (PA/QC), or by contract testing laboratories. This procedure does not apply to results generated for utility/facility monitoring (environment, water, etc.), process validation, or cleaning validation/verification.

3.0 Authority and Responsibility

3.1 The Director of Biopharmaceutical Process Analytics/Quality Control or designee has the responsibility for:

3.1.1 Defining this procedure.

3.1.2 Reviewing the OOS/OOT report for completeness and requesting additional testing as needed.

3.2 The Director of Biopharmaceutical Quality Assurance (BQA) or designee, has the responsibility for:

3.2.1 Reviewing the OOS/OOT report for completeness and requesting additional testing as needed.

3.2.2 Providing the final disposition of the product.

3.2.3 Trending of OOS/OOT events.

3.2.4 Quality oversight of this procedure.

3.3 The analyst(s), technician or operator who performed the testing resulting in an out-of-specification (OOS) result or the reviewer who discovers an out-of-trend (OOT) results is responsible for:

3.3.1 Immediately notifying his/her Supervisor or designee of the OOS or OOT results.

3.3.2 Participating in the investigation of OOS/OOT results.

3.3.3 Analysts may be required to implement corrective and preventive actions, when applicable, to prevent future occurrences of OOS/OOT results due to laboratory error.

3.4 Area Supervisors are responsible for:

3.4.1 Initiating an OOS/OOT investigation.

3.4.2 Participating in investigating the OOS/OOT event.

3.4.3 Assuring corrective and preventive actions are implemented when applicable.

3.4.4 Completing the required investigation report(s).

3.5 BQA is responsible for assigning the OOS/OOT investigation tracking numbers.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

3.6 The PA/QC Supervisor and/or the PA/QC Director are responsible for providing the conclusion(s) for the cause of the initial OOS/OOT result and approving the investigation report.

3.7 Production Managers are responsible for reviewing production records, as requested, to detect events that may result in the failure of a lot to meet established specifications.

4.0 Overview of the Process

Analytical testing is performed in a manner to yield accurate and reliable results. PA/QC test results that are out-of-specification (OOS), out-of-trend (OOT), or unexpected are investigated by the analyst and their supervisor to confirm that they accurately represent the quality attributes of the sample being tested. Investigations occur in two phases. The first phase of investigation attempts to identify “obvious” causes for the OOS/OOT result (such as out of calibration equipment, use of outdated reagents, calculation errors, etc.). If no obvious causes or error can be identified, the investigation is expanded to a second phase, often utilizing laboratory experiments, to identify a cause of the initial OOS/OOT result. Initial OOS/OOT results that are determined to be due to laboratory error are invalidated and after implementing corrective action to prevent a future occurrence, the sample may be retested. The retest result replaces the initial OOS/OOT result.

For investigations yielding an inconclusive cause for the OOS/OOT event, the sample may be retested in replicate with approval by the Director of PA/QC. Both sets of results (the initial OOS/OOT result and retest results) are used when dispositioning the lot. In addition, this procedure may be used to evaluate results that are unexpected or are part of a trend in results that may warrant additional further effort to determine their cause.

Investigations that indicate that the OOS/OOT result accurately represents the quality attributes of the sample, and are found to be valid, will result in an investigation being conducted into the manufacturing and storage of the product from which the sample was taken.

Contract testing laboratories may follow their own internal SOPs and associated documentation. PA/QC and BQA will review the vendor investigation documentation completed by the testing laboratory. A single BDP OOS/OOT tracking number is assigned to include the investigation conducted by the outside testing laboratory and the internal BDP review and or investigation of the vendor’s OOS/OOT event.

5.0 Considerations for Preventing OOS/OOT Results

5.1 Analyst Preparations before Conducting an Assay include that:

5.1.1 The procedure must be described in a written, approved document.

5.1.2 The analyst must have the appropriate training documented for conducting the assay.

5.1.3 Appropriate materials/supplies/standards must be used.

5.1.3.1 For example, materials must be within their expiration date, be appropriately stored, etc.

5.1.4 Equipment required for the assay must be within its calibration period and properly maintained.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

5.1.5 The sample to be assayed must be correctly identified and have been stored properly.

5.2 Analyst Performance of the Assay

5.2.1 The analyst must perform the assay following the written, approved procedures.

5.2.2 Work must be documented as it is performed.

5.2.3 Deviations in the performance of the assay must be documented and approved.

5.2.4 Obvious errors in the performance of the assay that would be suspected to cause an inaccurate result must cause termination of the assay as soon as the errors are noticed. Analysts should not knowingly continue an analysis they may have to invalidate later for an assignable cause.

5.2.4.1 Terminate the assay when an obvious error (such as dilution errors or known contamination of samples) occurs or is detected during the performance of an analysis prior to achieving a result. A new test may be initiated after correcting the conditions that caused the initial test to be terminated.

5.2.4.2 Errors and their corrections must be documented on test paperwork. Initial data must be maintained as part of the test record.

5.3 Reporting of a Value by the Analyst

5.3.1 Assay results must be reported only after the assay's system suitability requirements and controls have been evaluated and found acceptable.

5.3.1.1 For example, if reference standard results for a chromatographic analysis indicate that the system is not functioning properly, test samples shall not be analyzed until the problem is identified and resolved.

5.3.2 Analysts must check the data for compliance with specifications before discarding test preparations, standard preparations, or reagents. These solutions may need to be used in any retest or investigation that may be necessary. It is preferable to make additional dilutions from the original sample (retest) rather than resample.

5.4 Data Review by PA/QC and BQA

5.4.1 GMP/GLP analytical tests are reviewed by PA/QC and BQA for accuracy and completeness. If an OOS result or unexpected result is detected during review of testing results, the reviewer will immediately bring the result to the attention of the analyst and the BQC Supervisor to initiate the OOS investigation.

6.0 OOS/OOT Investigation Procedures

6.1 Initial Actions by Analyst

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

6.1.1 Immediate Notification: If an OOS, OOT, or unexpected result occurs, the analyst shall immediately notify the appropriate PA/QC Supervisor and the Director of PA/QC.

6.1.2 Test results which are in specification but potentially Out of Trend during product stability testing may not be discovered until the test result is compared to historical values as part of the stability review and reporting process. The stability analyst or reviewer shall immediately notify the appropriate PA/QC Supervisor and the Director of PA/QC upon the discovery of a potential OOT result.

6.1.2.1 Stability test results can be determined to be Out of Trend if there are at least two historical data points for comparison to the test value, including release / COA test results.

6.1.2.2 Putative OOT results from tests without a clear rate of change can be identified as significant using a 95% confidence interval range (±2 standard deviations) based on historical test and intra-assay replicate results. Non-significant results within the 95% CI are not considered OOT and can be documented in the QC test report.

6.1.2.3 Possible OOT results from a stability test which exhibits a clear trending value over time (but which is still within specifications) can be analyzed using regression analysis with a 95% CI range about the regression mean of each time-point. Non-significant results within the 95% CI trend-lines are not considered an OOT event and can be documented in the QC test report.

6.1.3 Unexpected test results are handled in a similar manner as an OOS or OOT as appropriate and are considered to be “unexpected” based on non-conformance to prior test data, projected results, or past experience.

6.1.4 Secure any remaining solutions, standards, dilutions, reagents, and samples. These materials should be segregated and not used for other testing until the OOS investigation is resolved.

6.2 Initial Investigation

6.2.1 Notification (within one workday): Notification (e-mail acceptable) will be made to the following people for OOS/OOT investigations that are entering the initial investigation phase:

- Director of Process Analytics/Quality Control
- Director of Quality Assurance
- Quality Assurance Manager
- Production Manager
- Project Scientist

Attach a copy of the notification to **Form 22004-01**.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

6.2.2 Timeframe: The initial investigation into an OOS/OOT must be initiated as soon after an OOS/OOT result is discovered as possible and completed within 30 days. When necessary, extended investigation periods must be approved by PA/QC. Justifications for investigation period extensions must be documented and notification submitted to BQA.

6.2.3 OOS Tracking Number: The PA/QC Supervisor will request an investigation number from BQA. This tracking number will be used, when needed, for the expanded investigation and any retesting. The tracking number follows the format "OOS-YY-###".

OOS: indicates that the number related to an out of specification or out of trend result

YY: the last two digits of the current year (for example 15 = 2015)

###: is a sequential number assigned to the event starting with 001 on January 1st of every year.

6.2.4 Investigation: An investigation will be conducted and documented following the prompts on **Form 22004-01**. An investigation must be conducted whenever an OOS/OOT test result is obtained to determine the cause of the OOS/OOT.

6.2.4.1 Review of System Suitability Criteria: The Supervisor and Analyst verify that system suitability acceptance criteria were met.

6.2.4.2 Review of Analyst Execution of the Assay: The Supervisor discusses the test procedure with the analyst to confirm the analyst's knowledge of and performance of the correct procedure as specified in the applicable SOP. The Supervisor will review the training files and records of the analyst involved to assure proper training has been accomplished.

6.2.4.3 Review of Raw Data and Calculations: The Supervisor and Analyst (and/or other knowledgeable persons) examine the raw data obtained in the analysis, including chromatograms and spectra, and identify anomalous or suspect information. Calculations in the analyst's notebook or worksheet are verified.

6.2.4.4 Equipment Suitability: The Analyst and the Supervisor will review the records of equipment used in conducting the test to assure that current calibration is in place and any maintenance conducted was performed correctly and has not disturbed the operation of the equipment. The equipment logs will be reviewed to detect activities that may impact the ability of the equipment to perform properly.

6.2.4.5 Suitability of Materials and Standards: The Analyst and Supervisor will review reference standards, solvents, reagents and other solutions to:

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

6.2.4.5.1 Confirm that they meet PA/QC specifications as listed on the raw material specification sheet. A review will be conducted, if necessary, of paperwork (Certificates of Analysis) as related to supplies used in the performance of the procedure.

6.2.4.5.2 Confirm that the reference standards and materials used in the testing process were properly identified and stored and used prior to expiration.

6.2.4.5.3 Confirm that reagents or solutions used in the execution of the assay were properly prepared.

6.2.4.6 Suitability of the Sample: The Analyst and Supervisor will confirm that the test sample was appropriately selected, properly stored and properly prepared for the test.

6.2.4.7 Suitability of the Environment: The Analyst and Supervisor will confirm that the environment, if applicable, is suitable for the execution of the test. Incubation chamber temperatures and conditions should be reviewed for appropriate environmental conditions.

6.2.5 Results of Investigation and Conclusion: The Analyst and Supervisor will document the results and conclusions of the initial investigation on **Form 22004-01**. One of the following categories is selected as a conclusion to the initial investigation.

6.2.5.1 Initial Investigation: Assignable Cause, Laboratory Error

"Initial OOS/OOT value resulted from an assignable laboratory cause and is, therefore, invalid. The test will be repeated after the non-conforming situation has been corrected."

A justification for this statement must be described, as well as the corrective action needed to address the non-conforming situation (for example, equipment calibration, analyst training, etc.).

6.2.5.2 Initial Investigation: Inconclusive Cause

"The cause of the initial OOS/OOT value remains inconclusive. An expanded investigation will be conducted."

Initial Investigation: Inconclusive Cause (testing for stability or on R&D materials)

(For results from stability testing or testing on R&D materials only).

The cause of the initial OOS/OOT value remains inconclusive. An expanded investigation is not warranted.

(This conclusion must be justified and documented.)

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Special considerations are in place for OOS/OOT results for stability testing. Products produced by the BDP do not typically have an established shelf life. Stability testing is performed to collect information to establish a product shelf life. There is no expectation that products will be stable indefinitely and at some point, if continued, stability testing will generate an OOS or OOT result. OOS/OOT stability results will be investigated with an initial evaluation; however, an expanded investigation may be determined to be unwarranted at the discretion of the PA/QC Director. The decision not to proceed to an expanded investigation along with the justification for this decision will be documented on the OOS/OOT investigation, **Form 22004-01**.

6.2.5.3 Other: (describe)

6.2.6 Review and Approval: **Form 22004-01** is reviewed and approved by the Analyst, Supervisor, PA/QC Director (or designee) and BQA Director (or designee).

6.3 Expanded Investigation

If the initial investigation does not determine a conclusive cause for the OOS/OOT result, an expanded investigation is automatically required and is documented on **Form 22004-02**. Test data generated during the expanded investigation will be labeled "INVESTIGATION: (OOS number"). (For example: "INVESTIGATION: OOS 15-013"). Any associated documentation will be attached.

6.3.1 Notification: Notification (e-mail acceptable) will be made to the following people for OOS/OOT investigations that are entering an expanded investigation phase:

6.3.1.1.1 Director of Process Analytics/Quality Control.

6.3.1.1.2 Director of Quality Assurance.

6.3.1.1.3 Quality Assurance Manager.

6.3.1.1.4 Production Manager.

6.3.1.1.5 Project Scientist.

6.3.1.2 Attach a copy of the notification to **Form 22004-02**.

6.3.2 Timeframe: The expanded investigation into an OOS/OOT must be conducted (when it is necessary) as soon after the completion of the initial investigation as possible and within 45 days of the OOS/OOT result, unless an extension is authorized by the Director of PA/QC. Extensions must be justified, documented, and notification summited to BQA.

6.3.3 OOS/OOT Tracking Number: The same tracking number is used as for the initial OOS/OOT investigation.

6.3.4 Investigation: An investigation will be conducted and documented following prompts on **Form 22004-02**.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

6.3.4.1 Review of Manufacturing Process Sequences: The PA/QC Supervisor or designee will request the Production Manager to review the lot's manufacturing records to detect processes that may have caused the OOS/OOT result, including sampling related issues. The Production Manager summarizes the results of the manufacturing record review which are forwarded to the PA/QC Supervisor (e-mail is acceptable) and included with the OOS/OOT Expanded Investigation documentation. Testing may be required to confirm or deny any suspected or potential cause.

For example, to investigate an OOS result for a failing sterility test, the Production Manager would review production processes that would affect product sterility (like filter integrity, environment during fill, collection of samples, etc.). An in-depth review of all sections of the batch record may be required as the investigation warrants.

6.3.4.2 Review of Past OOS Events: Relevant past OOS/OOT events are reviewed to detect trends in testing that could suggest a cause of the OOS/OOT event. Testing may be required to confirm or deny the potential cause.

6.3.4.3 Review of Test Results for Other Similar Batches: Test results for other similar batches are reviewed to detect trends in testing that could suggest a cause of the OOS/OOT event. Testing may be required to confirm or deny the potential cause.

6.3.4.4 Review of Test Data and Follow-up: Test data are reviewed to detect potential causes for an OOS/OOT event. Testing may be required to confirm or deny the potential cause.

For example, data that suggests a potential degradation of the sample can be confirmed by testing the initial (potentially degraded) sample in parallel with a new sample.

6.3.4.5 Review of Sampling Process: The process of sampling is reviewed including the selection of the sample container, the sampling process, sample storage and sample processing before testing.

6.3.4.6 Review of Test Standard and/or Test Specifications: The suitability of the test standard is reviewed. The establishment of the test specification is reviewed.

Examples:

A review of the reference standard preparation may reveal that it is unsuitable for comparison against the sample under test. If this condition can be corrected (for example, authorizing a different reference standard though a deviation or a revision of the test protocol) the sample may be retested after corrections are made.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

A review of how the test specification was derived may reveal that the specification should be adjusted. If the specification can be revised, the sample may be evaluated against the updated specification. Care should be taken to assure that specifications are not revised to accommodate an OOS/OOT result without strong, documented justification.

6.3.5 Results of Investigation and Conclusion: The Investigator will document the results and conclusions of the expanded investigation on **Form 22004-02**. Testing data, if conducted, will be attached. One of the following categories is selected as a conclusion to the expanded investigation.

6.3.5.1 Laboratory Error – Assignable Cause

"Initial OOS/OOT value resulted from a laboratory error of assignable cause and is invalid. The test will be repeated after the non-conforming situation has been corrected." A justification for this statement must be described, as well as the corrective action needed to address the non-conforming situation.

6.3.5.2 Sampling Error – Assignable Cause

"Initial OOS/OOT value resulted from a sampling error of assignable cause and is invalid. The test will be repeated after the non-conforming situation has been corrected." A justification for this statement must be described, as well as the corrective action needed to address the non-conforming situation.

6.3.5.3 Inappropriate Standard or Test Specification - Assignable Cause

"Initial OOSOOT value resulted from the selection of an inappropriate standard or test specification and is invalid. The test will be repeated after the non-conforming situation has been corrected." A justification for this statement must be described, as well as the corrective action needed to address the non-conforming situation.

NOTE: If an inappropriate standard material was used in the initial test, retesting of the initial sample may be conducted after the condition has been corrected. This may require an approved revision (or deviation) to the applicable testing protocol.

If an inappropriate test specification was authorized for the test, the initial result may be reevaluated against an approved, revised test specification. Care should be taken to assure that specifications are not revised to accommodate an OOS/OOT result without strong, documented justification.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

6.3.5.4 Manufacturing or Storage Error

"Initial OOS/OOT value resulted from a manufacturing or material storage error." A justification for this statement must be described. Quality Assurance will open a Material Review Board (MRB) investigation into the manufacturing issue. See ***SOP 21008 - BDP Material Review Board***.

6.3.5.5 Orthogonally Verified Degradation or Product Change

"Initial OOS/OOT value resulted from a change to the product which is observed by one or more orthogonal analytical methods independent of the OOS/OOT assay." A justification for this statement must be described and the orthogonal analytical data included. Quality Assurance will open a Material Review Board (MRB) investigation into the cause of the product quality change and the lot disposition.

6.3.5.6 Cause of the initial OOS/OOT result remains inconclusive

Retesting of the initial sample (according to Section 7.0, below) may be conducted with the approval of the Director, PA/QC. Retest results that continue to fail specifications will result in the initiation of an MRB investigation.

6.3.6 Review and Approval: **Form 22004-02** is reviewed and approved by the Investigator(s), Analyst, Supervisor, PA/QC Director (or designee) and BQA Director (or designee).

7.0 Retesting of Sample

7.1 Retesting Due to Invalidation of the Initial OOS Result:

When the initial OOS/OOT result can be invalidated based on known laboratory error, sampling error or an inappropriate standard, the initial sample can be retested after correcting the cause of the error from the initial testing. This retesting is performed with the initial sample (unless it has been compromised) and with the same number of replicates specified in the test procedure. While documentation of the initial OOS/OOT testing is maintained with sample testing records, the initial invalid result is not reported.

7.1.1 Unless a sample has been compromised or has insufficient volume, the retest is performed on the original sample (retest).

7.1.2 Test records must indicate if a new sample was obtained for retesting (resample).

7.2 Retesting When Cause of Initial OOS/OOT remains Inconclusive

7.2.1 Retesting of a sample without determining an assignable cause for the initial OOS/OOT result may only be conducted with the approval of the Director, PA/QC who will specify (before retesting occurs) the number of replicates that

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

will be required for retesting. The number of replicates may be determined based on the purpose of the assay, quantity of sample available, etc. Notification of the retest plan is submitted to BQA.

7.2.2 Retesting will be performed according to the following scheme. Test data generated will be labeled "RETEST: (OOS number"). (For example: RETEST: OOS-19-001).

7.2.2.1 An appropriately-trained analyst will repeat the assay in replicate (according to the number of replicates specified by the Director, PA/QC).

7.2.2.2 If the original sample has been compromised or there is insufficient volume, another sample may be used. Use of another sample must be indicated on test documentation.

7.2.2.3 Values from all replicates are evaluated for conformance to specification.

7.2.2.4 An OOS result for any replicate will cause the sample to fail its specifications. An MRB investigation will be initiated for the product failure including notification of the product's PI/clinical investigators, and an assessment of continued product use.

7.2.2.5 An OOT result for any replicate will result in an MRB review of the product stability program data, notification of the product's PI/clinical investigators, and an assessment of continued product use.

8.0 Reporting of Test Results

8.1 Retest Results from Invalidated Assays

If an original OOS/OOT result has been invalidated and the test repeated, the repeat result is the reportable result for the assay.

8.2 Retests from Investigation Testing

With approval, a retest result derived from investigation testing is the reportable result for the assay.

8.3 Retest Results from Assays where cause is Inconclusive (replicate retesting)

All test values from testing of the sample (initial OOS/OOT result and all replicate retesting of the sample) are reported on the QC Test Request. These results (including the original OOS/OOT result) are used in making decisions about the disposition of the lot or stability protocol. The decision for how to report the value on a lot's COA or stability report will be coordinated by the Directors of Process Analytics /Quality Control and Quality Assurance.

9.0 Documentation

9.1 Forms 22004-01, 22004-02 and 22004-03 (and any associated documentation) are kept in BQA and filed in the project file. BQA makes copies and distributes them to the PA/QC analyst to attach to the Quality Control Test Request.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

9.2 BQA archives OOS/OOT Investigations as per ***SOP 21407 - Records Retention***.

10.0 Definitions

10.1 **OOS** – Out-of-specification.

10.2 **OOT** – Out-of-trend

NOTE: OOT can also be used to indicate an Out-of-Tolerance result during calibration of equipment.

10.3 **Result** – Value that is recorded in a laboratory notebook or on a worksheet that indicates the outcome of an analysis.

10.4 **OOS Result** – A result that does not meet the pre-established specification.

10.5 **OOT Result** – A result that meets pre-established specifications but falls outside of an expected range based on historical values for that product lot.

10.6 **Unexpected Test Result** – A test result that occurs and does not fit within historical or trend analytical data and is not out-of-specification but which may be out-of-trend or otherwise unexpected.

10.7 **Specification** - Criteria that a drug substance, drug product, or process must conform to in order to be considered acceptable.

10.8 **Retest** – Reanalysis of the same sample that failed the first test.

10.9 **Resample** – The collection of another sample from the material that failed the first test.

11.0 References and Related Documents

11.1 **SOP 21407** *Records Retention*

11.2 **SOP 21008** *BDP Material Review Board*

11.3 Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, October 2006 (CDER).

12.0 Attachments

12.1 **Attachment 1** Flowchart of Investigation of OOS Results

12.2 **Attachment 2** Form 22004-01, Out-of-Specification Laboratory Test Result: Initial Investigation

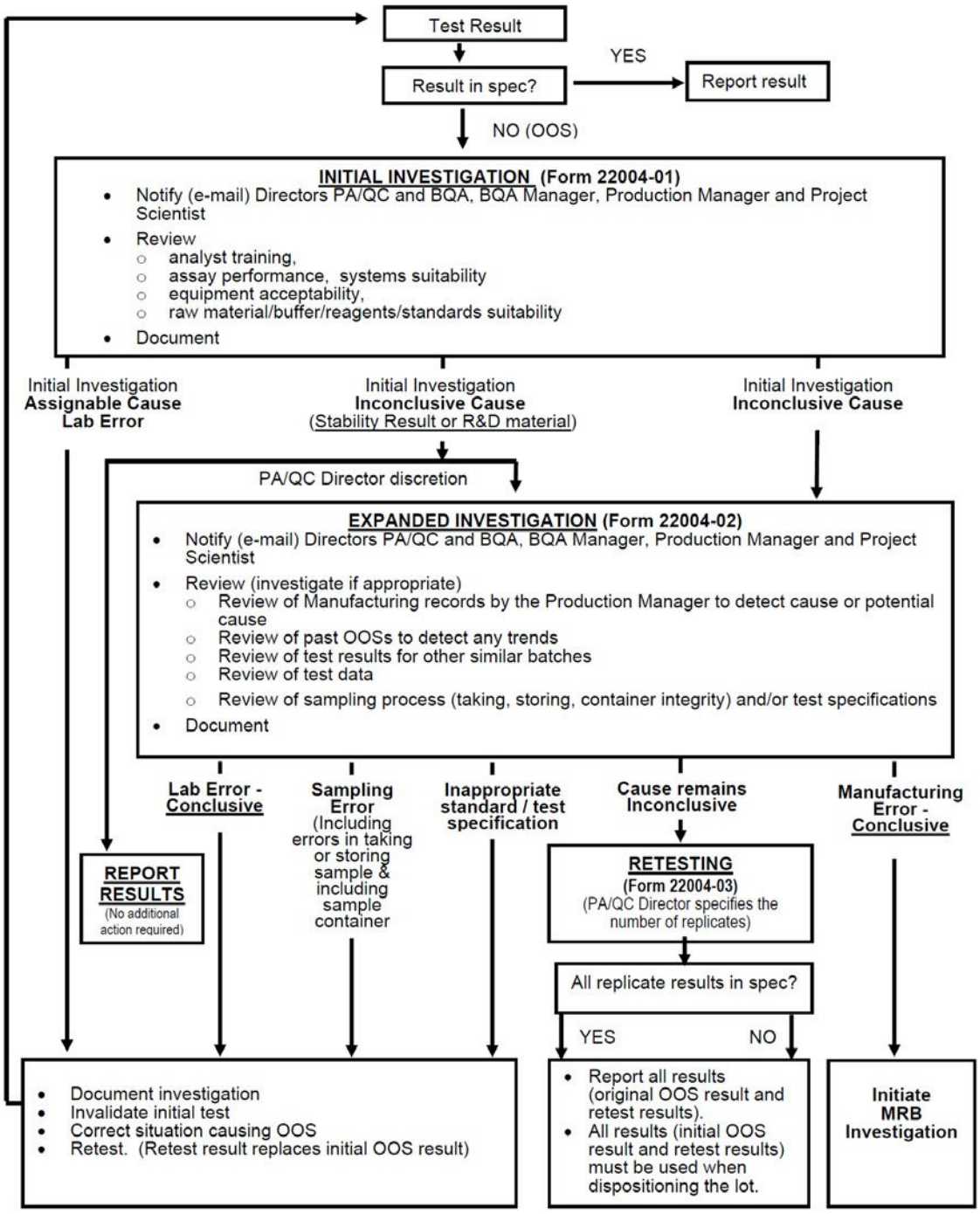
12.3 **Attachment 3** Form 22004-02, Out-of-Specification Laboratory Test Result: Expanded Investigation

12.4 **Attachment 4** Form 22004-03, Out-of-Specification Laboratory Test Result: Retesting of Sample

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

Attachment 1

Flowchart of Investigation of OOS/OOT Results



This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

Attachment 2
Form 22004-01, Out-of-Specification Laboratory Test Result: Initial Investigation

NCI-Frederick
Form No.: 22004-01
SOP No.: 22004
Revision 03: FEB 15 2019

O	O	S	-			-				I
Out of Specification Event			-	Last two digits of year		-	Sequential number starting each year on Jan 1			Initial Phase

OOS/UNEXPECTED LABORATORY TEST RESULT
INITIAL INVESTIGATION
Page 1 of 2

General Information ☐ Out of Specification (OOS) Result ☐ Out of Trend (OOT) Result ☐ Unexpected Result

Date of Occurrence: _____
Date Detected: _____
Date Due _____ (Due date is 30 days from date detected unless an extension is authorized by the PA/QC Director. Send extension notification to BQA)

QC Test Request #: _____ Sample No: _____
Sample Name: _____

Project Number; _____ Lot No: _____
BPR No: _____ Step Number: _____

SOP No: _____
SOP Title: _____
Specification: _____ Result: _____

Analyst: _____

Comments:
_____
_____
_____
_____

Investigative Procedure Checklist

Criteria	Evaluation S: Satisfactory U: Unsatisfactory N/A: Not Applicable	Comments
Notification Notify (e-mail) the following people that an OOS/OOT is entering the initial investigation phase: Directors, BQA and PA/QC, QA Manager, Production Manager, Project Scientist.		
Analyst Training Confirm that analyst has documented training on the current procedure. Validated assays require that analysts be certified in the procedure.		
Analyst Performance of the Procedure Through discussion with the analyst, attempt to confirm that the analyst performed the procedure as specified in the current SOP.		
Raw Data Review Confirm that raw data is appropriate, that data was correctly transcribed, that calculations were performed properly, that system suitability requirements have been met.		
Equipment Suitability Confirm that equipment used is within calibration and has been properly maintained. Review equipment logbook to identify any activities that may have compromised the equipment.		
Materials and Standards Confirm that materials, buffers, reagents, standards are suitable for use (appropriately selected, properly prepared, within expiration, properly maintained).		
Suitability of Sample Confirm that the test sample was appropriately selected, properly stored, and properly prepared for the test.		
Suitability of the Environment Confirm that the environment, if applicable, is suitable for the performance of the test. Incubation chamber temperatures and conditions should be reviewed for appropriate environmental conditions.		

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

Attachment 2 (Continued)
Form 22004-01, Out-of-Specification Laboratory Test Result: Initial Investigation

NCI-Frederick
Form No.: 22004-01
SOP No.: 22004
Revision 03: FEB 15 2019

O	O	S	-			-				I
Out of Specification Event			-	Last two digits of year		-	Sequential number starting each year on Jan 1			Initial Phase

OOS/UNEXPECTED LABORATORY TEST RESULT
INITIAL INVESTIGATION

Results of Initial Investigation (select one)

_____ **Initial OOS/OOT value resulted from a laboratory error of assignable cause and is invalid.** Test will be repeated after non-conforming situation is corrected.

Justification: Describe non-conforming condition and how it caused an OOS/OOT result.

Corrective Action: Describe corrective action required to address non-conforming situation (i.e., equipment calibration, analyst training, use of in-date standards, etc.).

_____ **The cause of the Initial OOS/OOT value remains inconclusive.** An expanded investigation will be conducted.

_____ **The cause of the Initial OOS/OOT value remains inconclusive.** An expanded investigation is not warranted. (Applicable to stability results and R&D material only).

_____ Other: Requires explanatory comment, below

Comments:

Review and Approval

Signature	Date
_____ Analyst	_____
_____ Supervisor, PA/QC (if applicable)	_____
_____ PA/QC Director	_____
_____ Quality Assurance	_____

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

Attachment 3
Form 22004-02, Out-of-Specification Laboratory Test Result: Expanded Investigation

NCI-Frederick
Form No.: 22004-02
SOP No.: 22004
Revision 03: FEB 15 2019

O	O	S	-			-				E
Out of Specification Event			-	Last two digits of year		-	Sequential number starting each year on Jan 1			Phase

OOS/UNEXPECTED LABORATORY TEST RESULT
EXPANDED INVESTIGATION

QC Test Request #: _____ Sample #: _____ Page 1 of 2

Date Initial Investigation concluded: _____
Date Expanded Investigation Due: _____ (Due date is 45 days from the close of the initial investigation unless an extension is authorized by the PA/QC Director – sent extension notification to BQA)

Investigative Procedure Checklist

Topic	Comments/Results Initials/Date (attach additional pages as needed)
Notifications Notify (e-mail) the following people that an OOS/OOT is entering the expanded investigation phase: Directors BQA and PA/QC, QA Manager, Production Manager, Project Scientist.	
Review of Manufacturing Process Sequence to detect processes that may have caused the problem (Production Manager). Summarize. Investigate to confirm or deny potential cause. Clearly label and attach any follow-up test results to this form. (An e-mail from the Production Manager or designee is acceptable.)	
Review of Past OOS Events to detect trends in testing that could suggest a cause of the OOS/OOT event. Clearly label and attach any follow-up test results to this form.	
Review of Test Results for Other Similar Batches. Test results for other similar batches are reviewed to detect trends in testing that could suggest a cause of the OOS/OOT event. Testing may be required to confirm or deny the potential cause. Clearly label and attach any follow-up test results to this form.	
Review of Test Data and Follow-up Test data are reviewed to detect potential causes for an OOS/OOT event. Conduct a laboratory investigation to confirm or refute this potential cause. Clearly label and attach any follow-up test results to this form.	
Review of Sampling Process Process of sampling is reviewed including the selection of the sample container, the sampling process, sample storage and sample processing before testing.	
Review of Test Standard and Test Specification The suitability of the test standard is reviewed. The establishment of the test specification is reviewed.	
Other	

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

Attachment 3 (Continued)
Form 22004-02, Out-of-Specification Laboratory Test Result: Expanded Investigation

NCI-Frederick
Form No.: 22004-02
SOP No.: 22004
Revision 03: FEB 15 2019

O	O	S	-			-				E
Out of Specification Event			-	Last two digits of year		-	Sequential number starting each year on Jan 1			Phase

OOS/UNEXPECTED LABORATORY TEST RESULT
EXPANDED INVESTIGATION

Page 2 of 2

QC Test Request #: _____ Sample #: _____

Results of Expanded Investigation (select one)

_____ **Initial OOS/OOT value resulted from a LABORATORY error of assignable cause and is invalid.**
Test will be repeated after non-conforming situation is corrected. (Complete Comments section)

_____ **Initial OOS/OOT value resulted from a SAMPLING ERROR of assignable cause and is invalid.**
Test will be repeated after non-conforming situation is corrected. (Complete Comments section)

_____ **Initial OOS/OOT value resulted from an INAPPROPRIATE STANDARD OR TEST SPECIFICATION assignable cause and is invalid.** (Complete Comments section)
Test will be repeated after the condition has been corrected. (Note, this may require a deviation to designate a different test standard or an approved revision to the document citing the test specification.

_____ **Initial OOS/OOT value resulted from a MANUFACTURING or STORAGE ERROR.**

An MRB investigation will be initiated.

_____ **Initial OOS/OOT value results from orthogonally verified DEGRADATION or PRODUCT CHANGE.**
An MRB investigation will be initiated.

_____ **Cause of initial OOS/OOT value remains INCONCLUSIVE.**

_____ Proceed to retesting with approval from the Director of PA/QC (Form 22004-03)

_____ Retesting not appropriate at this time (requires comment)
Comment:

COMMENTS

Justification: (describe non-conforming condition and how it caused an OOS/OOT result)

Corrective Action: Describe corrective action required to address non-conforming situation. (i.e., equipment calibration, analyst training, use of in-date standards, etc.)

Review and Approval

Signature	Date
_____ Analyst	_____
_____ Supervisor, PA/QC (if applicable)	_____
_____ PA/QC Director	_____
_____ Quality Assurance	_____

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

Attachment 4
Form 22004-03, Out-of-Specification Laboratory Test Result: Retesting of Sample

NCI-Frederick
Form No.: 22004-03
SOP No.: 22004
Revision 03: FEB 15 2019

`O	O	S	-			-				RT
Out of Specification Event			-	Last two digits of year		-	Sequential number starting each year on Jan 1			Phase

OOS/UNEXPECTED LABORATORY TEST RESULT
RETESTING OF SAMPLE

QC Test Request #: _____ Sample #: _____

Retesting

The investigation into the OOS/OOT has concluded that the sample requires retesting. If the cause of the OOS/OOT remains inconclusive, replicate testing of the sample is required. There may be some instances when testing performed as part of the investigation determined the cause of the initial OOS/OOT and that as part of that testing, the sample was adequately retested and those results are appropriate to stand as the retest result.

Retest Strategy (select one)

_____ **The cause of the OOS/OOT remains inconclusive**

The sample will be retested in replicate.

Retest Requirements

Number of Additional Sample Replicates: _____

PA/QC Director Approval: _____ Date: _____

Procedure

1) Perform a retest for the number of replicates specified above. If the same sample used in the initial testing is not available, or has been compromised, resampling is acceptable (and must be documented). Attach data and identify as "RETEST."
2) Evaluate each replicate result separately for conformance to specification.

Reporting of results (select one)

____ Retest replicate results each meet specification. All results will be reported on the QC Test Request and will be used with the initial OOS/OOT result in dispositioning the lot.

_____ At least one retest result failed specification. The sample FAILS its specification. An MRB will be initiated.

_____ **The retest result was generated as part of investigation testing.**

The sample was retested as part of the OOS/OOT investigation and the results obtained from the investigation testing are appropriate to stand as the final retest result. (Requires comment to describe which investigative test contains the accurate result for the sample and why the results are appropriate to stand as the final retest result).

Comment

Review and Approval

Signature	Date
_____ Analyst	_____
_____ Supervisor, PA/QC (if applicable)	_____
_____ PA/QC Director	_____
_____ Quality Assurance	_____

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].