Document Type:	Standard Operating Procedure (SOP)	**SOP Code:**	SOP-QA-006
Title:	Out of Specification (OOS) Investigations	**Version:**	1.0
Company:	NovaThera Pharmaceuticals Pvt. Ltd.	**Effective Date:**	2025-01-01
Location:	Pune, India	**Review Date:**	2026-01-01

Out of Specification (OOS) Investigations

Category: Quality Assurance

Standard Operating Procedure (SOP)

Company: NovaThera Pharmaceuticals Pvt. Ltd.

Department: Quality Assurance

Title: Out of Specification (OOS) Investigations

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1.0 PURPOSE

This procedure defines the requirements and responsibilities for investigating Out of Specification (OOS) test results obtained during the testing of raw materials, in-process materials, finished products, and stability samples at NovaThera Pharmaceuticals. This SOP ensures that all OOS results are thoroughly investigated to determine the root cause, implement appropriate corrective and preventive actions (CAPA), and maintain the integrity of pharmaceutical manufacturing processes. This procedure is designed to be compliant with current Good Manufacturing Practices (cGMP) and applicable regulatory guidelines.

2.0 SCOPE

This SOP applies to all analytical testing performed by the Quality Control (QC) laboratory at NovaThera Pharmaceuticals for all raw materials, in-process materials, finished products, and stability samples. It encompasses the investigation of any test result that falls outside the established acceptance criteria as defined in the relevant specifications, test methods, or regulatory filings. This SOP excludes OOS results arising from method development or validation activities. It is applicable across all product lines manufactured at the NovaThera Pharmaceuticals facility in Pune, India.

3.0 RESPONSIBILITY

QC Inspector:

- Identifies and reports potential OOS results immediately to the QC Supervisor.
- Performs initial assessment of the data for obvious errors.
- Assists in the laboratory investigation, as directed by the QC Supervisor.
- Ensures proper documentation of all observations and findings.
- Properly stores and labels retain samples.

Production Supervisor:

- Provides relevant information related to the manufacturing process for OOS investigations.
- Participates in the investigation to identify potential process-related causes of OOS results.
- Implements corrective and preventive actions (CAPA) related to the manufacturing process.
- Reviews and approves investigation reports related to production processes.

QA Manager:

- Oversees the OOS investigation process.
- Reviews and approves OOS investigation reports.
- Ensures that investigations are conducted in a timely and thorough manner.
- Tracks CAPA implementation and effectiveness.
- Identifies trends in OOS results and initiates appropriate actions.
- Ensures compliance with cGMP and regulatory requirements.

Head of QA:

- Provides final approval of OOS investigation reports and CAPA plans.
- Ensures that all OOS investigations are conducted according to this SOP.
- Oversees the overall quality system and ensures its effectiveness in preventing and resolving OOS issues.
- Reports OOS trends to senior management.
- Ensures appropriate communication of OOS investigations to regulatory authorities, if required.

4.0 MATERIALS & EQUIPMENT

PPE:

- Safety glasses
- Laboratory coat
- Appropriate gloves (nitrile, latex, etc. based on the material being handled)
- Face mask (if handling hazardous materials)

Equipment:

- Analytical balances (BAL-01, BAL-02)
- High-performance liquid chromatography (HPLC) systems (HPLC-01, HPLC-02)
- Gas chromatography (GC) systems (GC-01)
- UV-Vis spectrophotometer (SPCT-01)
- Dissolution apparatus (DIS-01)
- Tablet disintegration tester (DT-01)
- pH meter (PHM-01)
- Karl Fischer titrator (KF-01)
- Sifter (SFT-02)
- Blender (BLN-04)
- Tablet Press (TCP-01)

Documentation:

- OOS Investigation Form (QA-F-006-01)
- Laboratory Notebook (QA-R-001)
- Batch Manufacturing Record (BMR)
- Analytical Test Method
- Raw Material Specification
- Finished Product Specification
- Stability Protocol
- CAPA Form (QA-F-008)
- Deviation Report (QA-F-007)

5.0 PROCEDURE

5.1 Identification and Initial Assessment of OOS Result

5.1.1 The QC Inspector performing the analysis shall immediately notify the QC Supervisor upon observing a potential OOS result.

5.1.2 The QC Inspector shall document the OOS result and any relevant observations in the laboratory notebook (QA-R-001).

5.1.3 The QC Supervisor shall immediately review the data and consult with the QC Inspector to determine if an obvious error has occurred. Obvious errors may include:

- Incorrect sample preparation.
- Instrument malfunction (document equipment ID).
- Calculation error.
- Standard preparation error.

5.1.4 If an obvious error is identified, the QC Supervisor shall authorize the QC Inspector to repeat the analysis, documenting the reason for the re-analysis in the laboratory notebook.

5.1.5 If the re-analysis yields a result within specification, the original OOS result is considered invalid and the investigation is closed. The QC Supervisor shall document the error and the corrective action taken in the OOS Investigation Form (QA-F-006-01) and sign the form. The QA Manager then reviews the form.

5.1.6 If no obvious error is identified, or if the re-analysis confirms the OOS result, the QC Supervisor shall initiate a formal OOS investigation.

5.2 Phase 1: Laboratory Investigation

5.2.1 The QC Supervisor shall assign a qualified analyst to conduct the laboratory investigation.

5.2.2 The assigned analyst shall review the analytical procedure, instrument calibration records, and analyst training records to ensure that the method was followed correctly and that the analyst was properly trained.

5.2.3 The analyst shall examine the original sample preparation and analysis for any deviations from the established procedure.

5.2.4 The analyst shall re-analyze the original sample solution, if sufficient sample remains.

5.2.5 If the original sample solution is no longer available, the analyst shall prepare a fresh solution from the original sample and re-analyze it.

5.2.6 If the re-analysis confirms the OOS result, the analyst shall evaluate the integrity of the reference standard used in the analysis. This may involve preparing a fresh reference standard solution and re-analyzing the sample.

5.2.7 The analyst shall document all findings, observations, and re-analysis results in the laboratory notebook (QA-R-001) and the OOS Investigation Form (QA-F-006-01).

5.2.8 The QC Supervisor shall review the laboratory investigation findings and determine if the OOS result can be attributed to a laboratory error.

5.2.9 If the OOS result is attributed to a laboratory error, the QC Supervisor shall document the error and the corrective action taken in the OOS Investigation Form (QA-F-006-01). The investigation is then closed. The QA Manager then reviews the form.

5.2.10 If the OOS result cannot be attributed to a laboratory error, the QC Supervisor shall initiate a Phase 2 investigation, which includes a review of the manufacturing process.

5.3 Phase 2: Full Scale Investigation (Manufacturing Process Review)

5.3.1 The QA Manager shall be notified that a Phase 2 investigation is required.

5.3.2 The QA Manager, in consultation with the Production Supervisor, shall initiate a review of the Batch Manufacturing Record (BMR) for the affected

batch.

5.3.3 The Production Supervisor shall review the manufacturing process for any deviations from the approved manufacturing procedure.

5.3.4 The Production Supervisor shall investigate potential causes of the OOS result related to the manufacturing process, including:

- Raw material quality.
- Equipment malfunction (document equipment ID).
- Process parameters (temperature, pressure, mixing time, etc.).
- Operator error.

5.3.5 The QA Manager shall review raw material supplier information and Certificates of Analysis (COAs) for the raw materials used in the affected batch.

5.3.6 The Production Supervisor may request additional testing of retained samples of raw materials, in-process materials, or finished product from the affected batch.

5.3.7 The QA Manager shall review all relevant documentation and data to determine the root cause of the OOS result.

5.3.8 The Production Supervisor shall document all findings, observations, and test results in the OOS Investigation Form (QA-F-006-01).

5.4 Root Cause Analysis and CAPA

5.4.1 The QA Manager, in consultation with the Production Supervisor and the QC Supervisor, shall determine the root cause of the OOS result.

5.4.2 The QA Manager shall develop a corrective and preventive action (CAPA) plan to address the root cause of the OOS result and prevent

recurrence. The CAPA plan shall be documented in the CAPA Form (QA-F-008).

5.4.3 CAPA may include:

- Revising analytical procedures.
- Retraining analysts.
- Repairing or replacing equipment.
- Revising manufacturing procedures.
- Retraining production personnel.
- Implementing additional process controls.
- Supplier corrective action requests (SCAR).

5.4.4 The QA Manager shall assign responsibility for implementing the CAPA plan and establish a timeline for completion.

5.4.5 The QA Manager shall track the implementation of the CAPA plan and verify its effectiveness in preventing recurrence of the OOS result.

5.4.6 Effectiveness checks may include:

- Reviewing subsequent batch data
- Performing trend analysis
- Conducting audits of affected areas

5.5 Reporting and Documentation

5.5.1 All OOS investigations shall be documented in the OOS Investigation Form (QA-F-006-01).

5.5.2 The OOS Investigation Form shall include:

- Date of the OOS result.
- Product name and batch number.
- Test method and specification.
- OOS result.

• Summary of the investigation findings.
• Root cause of the OOS result.
• CAPA plan.
• Approval signatures.

5.5.3 The QA Manager shall review and approve the OOS Investigation Form.

5.5.4 The Head of QA shall provide final approval of the OOS Investigation Form and the CAPA plan.

5.5.5 All OOS investigation records shall be retained in accordance with the NovaThera Pharmaceuticals record retention policy.

5.6 Invalidating OOS Results

5.6.1 OOS results can only be invalidated with sufficient justification based on thorough investigation. The justification must be scientifically sound and documented.

5.6.2 An OOS result cannot be invalidated solely based on repeat testing within the sample set until passing results are obtained.

5.6.3 An OOS result that is determined to be a true reflection of the batch/material must be reported to regulatory authorities, if required.

6.0 POST-INVESTIGATION ACTIVITIES

6.1 The QA Manager shall ensure that the CAPA plan is implemented according to the established timeline.

6.2 The QC Supervisor shall monitor the effectiveness of the CAPA plan and report any deviations to the QA Manager.

6.3 The QA Manager shall conduct a periodic review of OOS trends to identify potential systemic issues and initiate appropriate actions.

6.4 The Head of QA shall review OOS trends and CAPA effectiveness as part of the annual product review.

6.5 If the OOS investigation reveals a potential product quality issue, the QA Manager shall initiate a risk assessment to determine the potential impact on product safety, efficacy, and quality. The Production Supervisor participates in this risk assessment.

6.6 Based on the risk assessment, the QA Manager may recommend additional actions, such as product recall or market withdrawal.

7.0 SAFETY PRECAUTIONS

7.1 All laboratory personnel shall wear appropriate PPE, including safety glasses, laboratory coat, and gloves, when handling samples and reagents.

7.2 All chemicals shall be handled in accordance with the Material Safety Data Sheet (MSDS).

7.3 All equipment shall be operated according to the manufacturer's instructions.

7.4 Waste materials shall be disposed of in accordance with the NovaThera Pharmaceuticals waste disposal procedures.

7.5 Report any spills or accidents immediately to the QC Supervisor.

7.6 In case of contact with chemicals, flush the affected area with water for at least 15 minutes and seek medical attention if necessary.

8.0 APPROVALS

Prepared By: QC Supervisor

Reviewed By: QA Manager

Approved By: Head of QA

Date: [Leave blank for manual completion]

Document Approval

Role	Name	Signature	Date
Prepared by:	_____	_____	_____
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Approved by (Head QA):	_____	_____	_____

Document Control Information

Document ID: SOP-QA-006

Version: 1.0

Effective Date: 2025-01-01

Next Review Date: 2026-01-01

Generated by: NovaThera SOP Generator System