## 1.0 Purpose

The purpose of this procedure is to describe the investigation process and documentation required when an Out-of-Specification (OOS) result has been generated. FDA regulations require that an investigation be conducted whenever an OOS test result is obtained (§ 211.192). The purpose of the investigation is to determine the cause of the OOS result.

## 2.0 Scope

This procedure applies to all laboratory test results that fall outside the specifications established by Giles, a customer or the USP compendium. Materials subject to laboratory tests include, but are not limited to, raw materials, in-process materials, final product, stability, and process validation.

The procedure used for management of materials which meet specifications but may not meet control limits or may possess characteristics undesirable for a specific customer (e.g. hard salt, crystal size, color, etc.) is the *Non-conforming Material* procedure *(Q12-PR-100-017)*.

## 3.0 Responsibility

The Quality Unit has overall responsibility for managing OOS investigations and documentation.

The Analyst is responsible for ensuring that only those instruments meeting established performance specifications are used and that all instruments are properly calibrated.

The Analyst is also responsible for immediately starting the initial assessment when an OOS is observed.

## 4.0 Safety Considerations

PPE requirements are to be observed in designated areas.

Safety is a condition of employment. Employees are not authorized to work in an unsafe manner and are prohibited from harming the environment of the facility or community.

## 5.0 Materials/Equipment

N/A

## 6.0 Procedure

The investigation of an OOS test result includes the laboratory phase of the investigation, additional testing that may be necessary, determination when to expand the investigation outside the laboratory, and the final evaluation of all test results. The source of the OOS results should be identified either as an aberration of the measurement process (a laboratory error) or an aberration of the manufacturing process. Even if a lot is rejected based on a test result, an investigation is required to determine if the result is associated with other lots.

The analyst detecting an OOS result must report that result promptly to the Director of Quality (or Designee). Together they will immediately conduct an investigation to determine the cause of the OOS result. The activities and results of the investigation are to be documented using *Out-of-Specification Investigation Report (Q13-PR-100-F025).*

### Phase I - Identifying and Assessing OOS Test Results – Laboratory Investigation

The first phase of the investigation includes an initial assessment to ascertain if the OOS result might be attributed to laboratory error. The following steps should be taken as part of the assessment:

1. Retain samples and test solutions until the investigation is concluded so that hypotheses regarding laboratory error or instrument malfunction may be tested using the same sample preparations.

2. Evaluate understanding of test method and performance of the correct procedure.

3. Examine the raw data obtained from the analysis and identify anomalous or suspect information.

4. Verify that the calculations used to convert raw data values into final test result are scientifically sound, appropriate, and correct; also determine if unauthorized or un-validated changes have been made to automated calculation methods.

5. Confirm the performance and calibration of instruments.

6. Determine that appropriate reference standards, solvents, reagents, and other solutions were used and that they met quality control specifications. Examine retained samples.

7. Evaluate the performance of the test method to ensure that it is performing according to the standard expected based on method validation data and historical data. This may include same analyst repeating the test and then a second analyst repeating the test (3x tests total).

8. Test hypothesis regarding what might have happened (e.g. dilution error, instrument malfunction).

9. Fully document and preserve records of the laboratory assessment.

- When clear evidence of laboratory error exists, laboratory test results should be invalidated. The OOS result is recorded in the laboratory notebook with suitable explanation and repeat testing can be performed. The initial OOS result is not considered in the final release of the material. Following any corrective actions indicated by the investigation, repeat testing (1x) and record results. The repeat results are considered in the final disposition of the material.

- When evidence of laboratory error remains unclear, a full-scale OOS investigation should be conducted to determine what caused the unexpected results.

    - In the case of an OOS result of vendor supplied materials, the materials will be returned to the vendor and a Supplier Complaint filed with the vendor.

Laboratory error is relatively rare. Frequent errors suggest a problem that might be due to inadequate training of analysts, poorly maintained or improperly calibrated equipment, or careless work. These trends will be appropriately monitored and reported by Quality to ensure any problematic areas are addressed.

**Phase II – Investigating OOS Test Results – Full-Scale OOS Investigation**

When the initial assessment does not determine that laboratory error caused the OOS result and testing results appear to be accurate, a full-scale OOS investigation is conducted. This investigation includes a review of the production records/events, sampling procedures, and possibly additional laboratory testing. The objective is to identify the root cause of the OOS result and take appropriate corrective and preventive action.

The Quality Unit will review the records and documentation of the manufacturing process with Production, Engineering, and Maintenance. A written record of the review is recorded on the *Out-of-Specification Investigation Report* and should include the following information:

1. A clear statement of the reason for the investigation.

2. A summary of the aspects of the manufacturing process that may have caused the problem.

3. The results of a document review, with assignment of actual or probable cause.

4. The results of a review made to determine if the problem has occurred previously.

5. A description of corrective actions taken.

If this part of the OOS investigation confirms the OOS result and is successful in identifying its root cause, the OOS investigation may be closed and the product rejected. However, a failure investigation that extends to other lots that may have been associated with the specific failure must be completed following the *CAPA Procedure (Q13-PR-100-014).*

**Concluding the Investigation**

The OOS investigation should be completed within 30 calendar days from the discovery of the OOS result. Justification should be presented and documented when completion by the deadline is not possible.

When an OOS result is generated regarding a distributed product that could result in a Serious Adverse Event, a field-alert report must be issued to the FDA within72 hours of the discovery of the OOS result. See *Recall/Withdrawal (Q12-PR-100-013).*

Completed OOS Investigations that have been closed will be maintained by the Quality Unit and filed in the cGMP Library for a period of at least 4 years.

## 7.0 Reference Documents

*Out-of-Specification Investigation Report (Q13-PR-100-F025)*
*Non-conforming Material (Q12-PR-100-017)*
*CAPA Procedure (Q13-PR-100-014)*
*Recall/Withdrawal (Q12-PR-100-013)*

## 8.0 Change Information

New Document