

Standard Operating Procedure

Title: Laboratory Results Out of Specification Investigation

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- 2.1. **Raw materials:** Samples to be retested include the original pooled sample, a resample of the bulk material and a previously passed retention sample.
 - 2.2. **Finished Goods:** Samples to be retested include the original set of samples (if available), a resample of the entire load, a recently passed batch from retention samples and a stability sample of the same finished goods code.
 - 2.3. **Stability, Trial, Process Validation and Complaints:** Samples to be retested include the original set (if available) or additional samples from the stability or trial batches and, if applicable, a retention sample of the same solution or finished goods code.

The original test preparation may be used as one of the samples for a retest.
 - 2.4. The number of samples required for a relative quantitative retest is nine (9), tested in duplicate. In cases where there are not enough samples available, the maximum number of samples available should be used.
 - 2.5. For empirical quantitative tests, e.g. pH, specific optical rotation, colour of solution, refractive index, etc., the number of retests is three (3) or as specified for pH by Laboratory Manager.

3. Procedure for Retest

Based on the type of analysis to be performed, the retest will follow an outlined procedure (part C) of the OOS Investigation Report.

3.1. Quantitative External Standard

This category covers any test which generates a quantitative result determined by comparison to a standard reference material, e.g. HPLC, UV-Vis, etc.

3.1.1. Two dilutions from a common stock standard or two duplicates from a common stock standard **IS NOT ACCEPTABLE**. Prepare either two independent standard preparations or if a standard preparation exists, prepare one additional standard preparation. It is essential that each standard be prepared individually.

3.1.2. Ensure that the instrument is in calibration and that all system suitability tests have been run.

3.1.3. Each standard preparation is analysed before the retest samples are analysed.

3.1.4. The relative error between the two standard preparations is calculated by the following formula:

$$\text{Relative Error} = \frac{200 \times (C1/r1) - (C2/r2)}{C1/r1 + (C2/r2)}$$

Where C1, C2 = the concentrations of std preparation 1 & 2 respectively
r1, r2 = the average responses for standard preparation 1 & 2 respectively.

The relative error must not be more than 2.0%. If the error is greater than 2.0% discard the standard preparations and repeat using two new standards.

If a realistic precision cannot be attained an analyst may proceed with the consent of the Laboratory Manager.

3.1.5. Calculate the result for each retest. These are the reported values.

3.1.6. **Acceptance Criteria.** If the results are within specification then a classification of acceptance is given.

Rejection of data

(i) If an aberrant result is known to be caused by Laboratory error, the value can

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3.3.3. Apply point 3.1.5, 3.1.6 and 3.1.7 for either accepting, accepting non-conforming and rejecting empirical measurements.

3.4. **Semi and Non Quantitative Method**

Examples include Thin Layer Chromatography (TLC) and Identifications (Infra-red, Ultra Violet, precipitation/colour change, etc).

3.4.1. For instrumental methods, verify the state of calibration of the instrument making the measurement.

3.4.2. Three retest samples are to be prepared independently.

3.4.3. Review the results for each of the three Retest Samples.

3.4.4. Apply point 3.1.5, 3.1.6 and 3.1.7 for either accepting, accepting non-conformity and rejecting semi- and non-quantitative methods.

4. **Reporting of results**

4.1. All results are reported electronically on an OOS investigation and report form (**Form-305/ Form-310**) along with the discussion of any pertinent information regarding the analysis, which have a bearing on the decision-making process, which is then incorporated into the Deviation Report.

The Incident Meeting investigation is to be thorough, unbiased, well documented and scientifically defensible.

Investigation of the Production Process (Part D of OOS form) assists the analyst to explain the OOS result and is part of the decision-making process to accept or reject a result.

Stability Trends are filed in the Product Technical Documents held in Technical Department.

4.2. The OOS Investigation and Report Form is forwarded electronically to the Quality Assurance Officer as supporting data when an Incident Meeting is called.

4.3. The OOS Investigation and Report Form is supporting data in the discussion of changes in production processes or analytical procedures and is forwarded to the Technical Manager for further action when required.

4.4. Results and final decisions should be recorded in the Laboratory Notebook according to **SOP LAB-025**

5. **Extended Investigation**

When the laboratory investigation does not determine that laboratory error caused the OOS result and testing results appear to be accurate, an Incident Meeting is held.

As part of the OOS investigation, a general review provides a list of other batches and products possibly affected and if the problem has occurred previously.