Standard Operating Procedure

Title: Initial Investigation of Out of Specification (OOS) Results in Microbiological Laboratory

Department	Micro Laboratory		Document no	MICLAB 145	
Title	Initial Investigation of Out of Specification (OOS) Results in Microbiological Laboratory				
Prepared by:		Date:		Supersedes:	
Checked by:		Date:		Date Issued:	
Approved by:		Date:		Review Date:	

1.0 **DOCUMENT OWNER**

Laboratory/Quality Manager

2.0 **PURPOSE**

To establish a procedure for the investigation of initial out-of-specification (OOS) or questionable results which have been generated for the product or material being tested.

3.0 **SCOPE**

3.1 This procedure applies to test results generated for raw materials, in-process materials, stability and finished products tested for medicinal products for commercial sale.

3.2 This procedure applies to test results generated for release, stability, in-process and retained samples associated with a complaint investigation.

3.3 This procedure does not apply to results generated by testing not described in 3.1 or 3.2 or out of specification results for process water and environmental samples.

3.4 An investigation for out-of-specification or questionable results must be initiated when an analysis has been performed on the sample in question.

3.5 Instances of out-of-specification or questionable results, where assignable cause is not readily apparent shall be investigated in accordance with the requirements described in this procedure.

3.6 If assignable cause is readily apparent, the occurrence is documented using the Laboratory Investigation Report (LIR) form, as applicable.

3.7 All LIR's must be completed and fully approved within 30 business days of the discovery of the initial OOS or questionable result. If laboratory investigation goes beyond 30 business days, an interim status report must be issued to the QA Manager.

3.8 All LIR's should be reviewed once per year to determine if trends are observed that require further action

- Immediately notifying the Microbiology Team Leader or the Lab Manager of any microbiological test result which does not meet specification or which fits the description of a questionable test result.

5.0 PROCEDURE

5.1 Discovery of out-of-specification or questionable result.

5.1.1 Upon discovery of any OOS or Questionable Result, the Lab Analyst shall immediately, before initiating any repeat testing, or retesting take the following actions:

- report the results to the Lab Team Leader or Lab Manager;
- document findings;
- document obvious errors (e.g., spilling of solutions or incomplete transfer of sample or standard), if known;
- retain all original samples and test preparations, such as sample solutions, standard solutions, glassware, microbiological culture media, and reagents used in the analysis and subsequent investigation, to the extent possible, until the initial investigation is completed; and
- retain samples and associated test preparations, when possible, in a manner that ensures their integrity (e.g., refrigerated) until the test article receives a final disposition.

Note: The Lab Team Leader shall determine if obvious errors (e.g., calculation or dilution errors) exist that might have caused the OOS or Questionable Result. If an obvious error is found, the OOS or Questionable Result is considered an invalidated result and no further investigation is required, unless the error would impact other testing. If obvious errors are not found, the Lab Team Leader shall initiate a further investigation.

5.1.2 The analyst ensures that an entry into the laboratory investigation database (online) or if this database is not available, an entry into the log book (manual system) is made and that a unique number is assigned to the laboratory investigation report. At this time, the analyst and team leader or designate completes section 1 (general information) of the laboratory investigation report. In cases where more than one lot of material is investigated for the same problem, only one investigation report is required. All affected lots must be clearly listed.

5.1.3 All Laboratory Investigation Reports are assigned a unique number. In cases where the online system is used, the number is assigned automatically by the database system and is denoted by the following format:

- (YYYYMMXXX, where YYYY and MM are representative of the computer system date's year and month respectively and XXX is uniquely allocated a sequential number applied based on the month and year.

5.2.3 If, in the Micro Team Leader's judgement, assignable cause is identified for an OOS or questionable result, the original result is invalidated. The assignable cause shall be documented in the LIR Form Section III "Initial Investigation" and Section IV "Findings/Conclusions from Initial Investigation" within one business day of discovery of the result. Testing is then repeated to generate valid results.

5.2.3.1 The analyst completes Section VII of the Laboratory Investigation Report: Retest Protocol. The Microbiology Team Leader approves the retest protocol. Retest is conducted as per the approved protocol.

The OOS or Questionable Result may be accepted as valid following the initial investigation with no further retesting.

If there is no readily apparent assignable cause the investigational measurement protocol (IMP) (section V of the laboratory investigation report) is prepared and signed by the team leader or designate.

The purpose of conducting investigational measurement is to determine an assignable cause. This section should only be completed when a suitable protocol is decided. Data generated during and investigational measurement is for investigation only and shall not be used as a valid test result.

5.2.3.2 On the Laboratory Investigation Report, the Micro Team Leader delegate/ completes Section VIII: Results of Retest, Section IX: Overall Conclusions and if corrective action is required, Section X: Corrective Action Plan.

The potential impact on other samples tested during the initial testing must be evaluated when an assignable cause is found. All related test results must be assessed for validity. A statement documenting the assessment and the decision must be included on the LIR Form Section III "Review of Testing Parameters", or Section IV "Findings/Conclusions from Initial Investigation".

5.2.3.3 If, in the Lab Manager's judgment, no readily apparent assignable cause is determined by the initial investigation, it may be necessary to issue an Alert report to notify others of the situation. The Lab Manager shall determine whether an alert report is needed and notify the QA Manager that an alert report is needed. The QA Manager shall ensure that such reports are issued within one business day following the completion of Section IV of the LIR form.

5.3 **Assignable Cause.**

5.3.1 Test Results, whether In- or Out-of-Specification, that are obtained under the following conditions must be invalidated and the test repeated. These are examples of the classifications that are included on the LIR Form to document types of assignable causes:

- Sample – The original sample was contaminated or insufficient in quantity;
- Method/Documentation – Unclear test method for Standard Operating Procedure directions which resulted in incorrect test execution;
- Analyst Error – Examples include, but are not limited to:

5.6.2 Obtaining additional stability samples is permitted for confirmatory purposes. However, when possible, the sample that was the source of the initial OOS or Questionable Result must also be included in the retest plan.

5.6.3 All stability samples from the same packaging lot and stored under identical conditions are considered equivalent for the resample purposes.

5.7 **Evaluation of results.**

5.7.1 If an assignable cause is associated with the original OOS or Questionable Result, the original result is invalidated and the impact of the assignable cause on other samples in the test must be determined.

5.7.2 Data from the original sample shall be retained in the test record, invalidated, and not included in the batch disposition decision when an assignable cause has been established.

5.7.3 If no assignable cause is found to be associated with the original OOS, and retesting is performed, all test results shall be documented on the LIR, forwarded to the QA Manager, and considered in batch/lot release decisions.

5.7.4 If the test method is shown by investigation to be in question, a general review of the method must be conducted, and required corrective action taken. Corrective action is to be recorded on the LIR form.

5.8 **Reporting Results.**

5.8.1 Invalidated OOS Results shall not be averaged with retest results for reporting purposes.

5.8.2 LIR Form Section VIII "Repeat/Retest Results" shall be used to report results [i.e., the value determined to be the final valid results (e.g., the retest results, or the confirmed initial OOS)].

5.8.3 Upon completion of the Laboratory Investigation for initial OOS results, the Laboratory Manager determines if the QA Manager needs to issue an Alert report.

5.8.4 A confirmed OOS microbiological test result shall result in rejection of the test article.

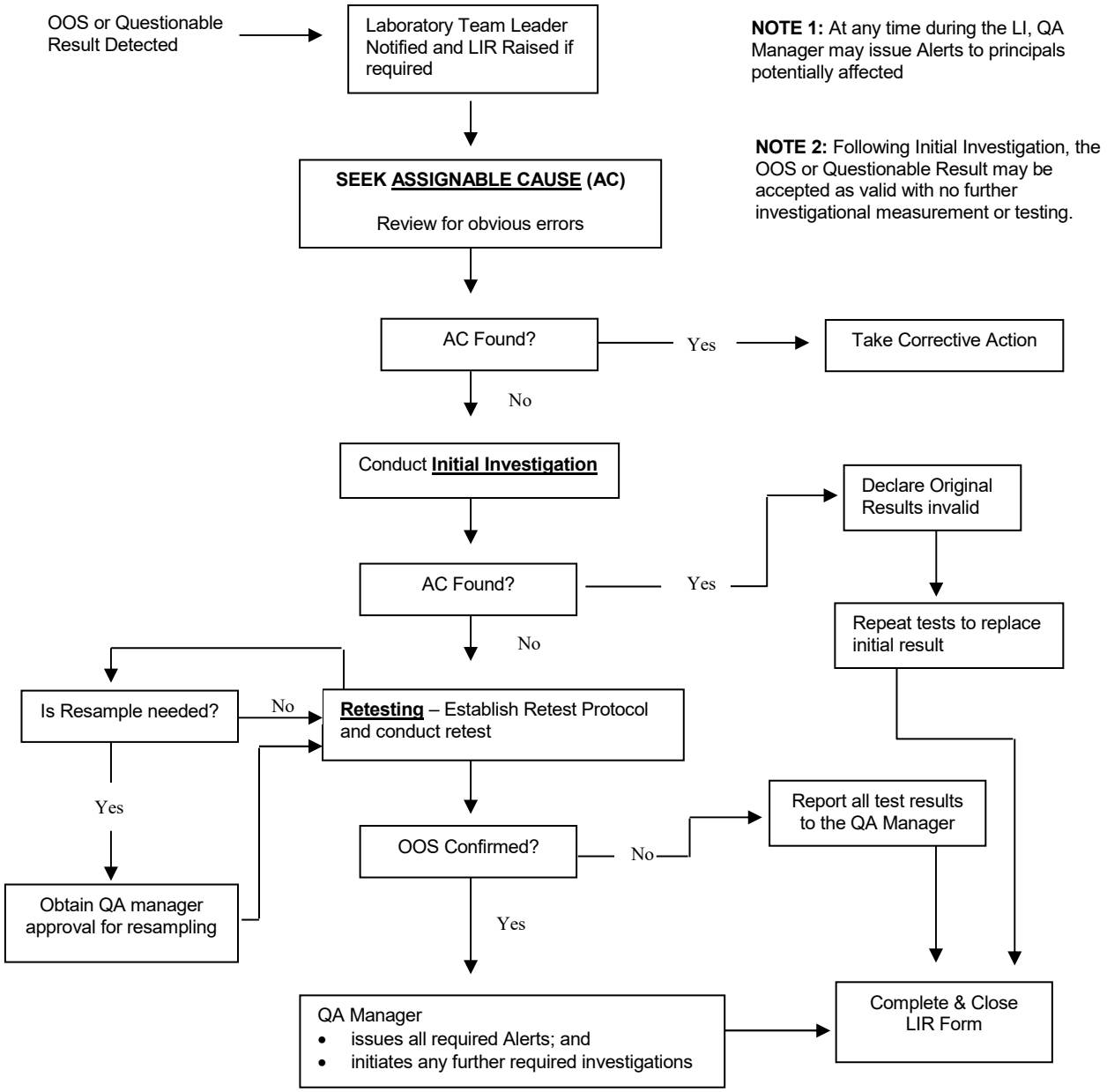
5.8.5 In the event of a confirmed OOS Result, it may be necessary to issue an alert report to other departments within the site to notify them of the situation. The QA Manager shall ensure that such reports are issued within one business day following confirmation of an OOS Result.

The QA Manager shall also evaluate the need for an investigation into the source of the confirmed OOS result and ensure that such investigations are completed.

5.8.6 The QA Manager shall inform the Senior Management Team (QO Manager, Production Manager and the Operations Director) which shall determine if the issuance of any reports responsible for notifying the Area Quality Review Team (A-QRT) in the event of any proposed market Action (eg. Product Recall) or stop distribution notice.

5.9 **Closing the Laboratory Investigation.**

LI Process Flowchart



6.4.3 When serial dilutions are plated, higher number of CFU's are recovered from higher dilutions.

6.4.4 Micro-organism recovery is obtained on selective medium but no growth is obtained on non-selective medium, both coming from the same broth preparation.

6.5 **Resample:**

A new sample obtained from previously sampled batch.

6.6 **Retest:**

Additional testing on the original test sample. Re-testing is only appropriate after a Microbiological Laboratory Investigation has been completed, and where an assignable cause has been identified for an OOS result during a Microbiological Laboratory Investigation.

6.7 **Out of Specification Result:**

A single determination of a test sample that does not conform to established specification.

6.8 **Analyst Error**

Situations where OOS or questionable data are the result of a failure to comply with the approved procedure or an error during the analysis. Examples include the following; improper test procedure, contamination through the use of non-sterile equipment, media, diluents etc.

7.0 RELATED DOCUMENTS

Form 690 – Laboratory Investigation Report Form

8.0 SUMMARY OF CHANGES

Version #	Revision History
MicLab-150	New

