

Standard Operating Procedure

Title: Microbiology Laboratory Investigation and Retest Procedure for Atypical and Out-of-Specification Results

Out of Limit (OOL)	Out-of-Limit result is a result that exceeds a pre-determined alert limit, which is applied to a sample type in order to assess whether a process is in control. The result exceeds alert limits.
Atypical Test result (ATR)	A test result that based on trending data, falls outside of the historical range for the sample/product but is within sample/ product specifications. The result passes but may indicate process drift.
Deviation Report (DR)	Documentation system for recording, investigation and analysing material and processes that do not comply with company requirements.
Known Laboratory Error (KLE)	This is a laboratory deviation that is known to be caused by technician or instrument failure. A KLE, which occurs during test set-up and prior to generation of the results, does not require a DR or Form 690 .

Investigational Testing	Testing conducted to assist in the determination of the root cause of and OOS or ATR. Investigational testing must be given prior approval by Microbiology Manager and documented on Form 690 and in DR is appropriate. Results from investigational testing can only used to determine whether the OOS result is valid.
Repeat Test	This is a test that is designed to replace a valid test that has been shown to be invalid, through the investigation process described in this procedure. Once an assignable cause has been established, the discrepant result is invalidated and a repeat test is performed using the original test procedure and the original sample whenever possible.
Investigational Testing	Testing conducted to assist in the determination of the root cause of an out of specification or atypical result. Investigational testing must be documented and approved by Microbiology Manager. Results from investigational testing are only used to determine whether the OOS result is valid.
Retest	Additional testing performed using an approved retest protocol as outlined below.
BPN	Batch Production Number
BSB	Bulk Solution Bioburden Samples
FCB	Filled Container Bioburden Samples
RM	Raw Material

Related Documents

Form 690	Microbiology Out of Specification (OOS) Investigation and report Form
MICLAB 060	Micro Laboratory Procedure for Sterility Testing
MICLAB 085	Bacterial Endo Toxin Testing kCA Method
MICLAB 075	Micro Evaluation on Bioburden, Non sterile and Raw Materials
MICLAB 080	Bacterial Endo Toxin Testing (LAL) - Gel Clot Method
MICLAB 055	Microbiological Monitoring of Plant Water Systems
QMS 035	Deviation Reporting System

EHS Statement

Not applicable

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NOTE: When considering whether re-testing or confirmatory testing is valid, any factors that may potentially affect the sample quality should be considered, including but not limited to the age and storage conditions of the original or retention sample and whether the sample type has inherently antimicrobial characteristics. In some cases, re-testing a retention sample may be of no value, and other criteria should be assessed in the context of product release.

- 2.8 Repeat testing or confirmatory/ investigation testing is initiated only when approval from Micro Manager has been granted.
- 2.9 Where repeat testing, re-testing or confirmatory testing is conducted, Section C of **Form 690** must be completed, including the number of replicates used for testing, the acceptance criteria for the additional test results and the justification and reason for conducting the additional testing. When re-testing refer to Section 5 for determination of the re-test protocol.
- 2.10 Results from other testing are recorded in Section C of **Form 690**.
- 2.11 If a batch or partial batch is rejected as a result of the out of specification investigation, a level 1 Investigation should be carried out.
- 2.12 Included in Phase 2, Section C of **Form 690** is the batch disposition as well as the corrective and preventative actions when applicable.
- 2.13 The action plan is reviewed by the Laboratory Manager, or the delegates and the Technician.

3. Initiating Form 690

- 3.1 For each Action or Alert Limit excursions within the scope of this procedure, a Microbiology Laboratory OOS/OOL Investigation and Report **Form 690** is to be initiated.
- 3.2 Each OOS/OOL Investigation Report form must be assigned a unique identifying number. This number should be referenced in any relevant DR or Investigation Reports associated with the OOS/OOL result.
- 3.3 The OOS/OOL Investigation report form should be attached to the DR reference where appropriate, and filed in the Microbiology Laboratory Investigations file.

4. Laboratory Investigation Process

4.1 General

- 4.1.1 In the initial instance of recording an OOS/OOL result, notify Microbiology Manager and/or appropriate delegates.
- 4.1.2 A test may be repeated when the Initial test has been invalidated due to an error in procedure, (including Technician or equipment failure, or test acceptance criteria not met).
- 4.1.3 Microbiology Laboratory Investigations will be conducted in two phases - **Phase 1** and **Phase 2** as detailed below. **Phase 1** is the review of the testing procedures by the microbiology technician to eliminate the possibility of laboratory introduced error or contamination. **Phase 2** will investigate the OOS result in more detail.
- 4.1.4 Under normal conditions Alert Level excursions (OOL) will only require **Phase 1** and if result is deemed valid, microbial identification and simple trend reports should be conducted. No DR is required for OOL results. Specific Test

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- 5.4.2 **Non-Sterile Bioburden Samples (RM, FCB, BSB, Water)** – Perform a retest in triplicate on the original sample and on a retain sample if available.
- Where original result has been invalidated (Phase 1), re-test of original sample, using original sample size should be conducted.
 - If retests of both original and retain sample confirm the original result, report the initial result.
 - If retest do not confirm the initial result, document results of the retests on **Form 690** (Phase 2, Section C); no further testing is permitted. Microbiology Manager or delegate will evaluate all result in order to determine which results will be reported.
- 5.4.3 **Endotoxin Samples** – Refer to test specific procedure in relation to the number of re-tests to be performed.
- 5.4.4 Where original result has been invalidated (Phase 1), re-test of original sample, sample should be conducted.
- 5.4.5 Where original result is deemed valid, additional investigational testing may be permitted.
- 5.4.5.1 If retest of both original and retain samples confirm the original result, report the highest value obtained (i.e. worse case)
- 5.4.5.2 If any of the following scenarios occurs, all results should be documented on **Form 690** (Phase 2, Section C); no further testing is permitted. Microbiology Manager or delegate will evaluate all result in order to determine which results will be reported.
- Retest of original sample confirm original result but retain sample retest results are different from original result.
 - Retest results of both original and retain samples are different from original results.
 - Retest of retain sample confirm original result but original sample retest results are different from original result.
- 5.4.6 **Sterility Test** - Retesting (using additional samples or retain samples) is only permitted where there is unequivocal evidence which invalidates the sterility test. Refer to **MICLAB 060** for further guidance.

Note: If there is not a sufficient quantity remaining from the original sample for additional testing, new samples should be selected by sampling throughout the batch using the original sample plan.

Microbiology Out of Specification (OOS) Investigation and Report Form

(Ref. MICLAB 110)

Phase 1

Out of Specification Result
(Action Level Excursions) ☐

Out of Limits Result
(Alert Limit Excursions) ☐

PART A – Product or Sample Details

Form Initiated by:		Unique Identifier	
Product Description		DR Number	
Batch Production Number (BPN)		Product Code	
Original Test Result		Limits/ Specification	
Micro Manager Notified	Yes <input type="checkbox"/> No <input type="checkbox"/>	By who?	Initial and Date

PART B – Evaluation of Laboratory Testing

Test Type	(tick)	SOP Reference	Control Method reference (if applicable)
Non-Sterile Testing	<input type="checkbox"/>	MICLAB 075	
Water	<input type="checkbox"/>	MICLAB 055	
Sterility Testing	<input type="checkbox"/>	MICLAB 060	
Endotoxin	KCA <input type="checkbox"/>	MICLAB 085	
	GEL <input type="checkbox"/>	MICLAB 080	
Other	<input type="checkbox"/>		
Name of Technician who performed the test		Training records complete	Yes <input type="checkbox"/> No <input type="checkbox"/>
Date Sampled		Date Test performed	
Was test conducted in accordance with SOP & Control method	Yes <input type="checkbox"/> No <input type="checkbox"/>	If No, comment:	
Media/Reagents Used	Lot Number	Expiry Date	Passed QC Checks
			Yes <input type="checkbox"/> No <input type="checkbox"/>
			Yes <input type="checkbox"/> No <input type="checkbox"/>
			Yes <input type="checkbox"/> No <input type="checkbox"/>
			Yes <input type="checkbox"/> No <input type="checkbox"/>
			Yes <input type="checkbox"/> No <input type="checkbox"/>
			Yes <input type="checkbox"/> No <input type="checkbox"/>