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ANNEX 3 – VERIFICATION OF OOS RESULTS
ANNEX 3.1 GENERAL INTRODUCTION – VERIFICATION OF INITIAL OUT-OF-SPECIFICATION RESULTS

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GENERAL INTRODUCTION - VERIFICATION OF INITIAL OUT-OF-SPECIFICATION (OOS) RESULTS

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1. Introduction

The objective of this Annex is to describe the steps to follow for the management of out-of-specification (OOS) testing results. The failure investigation may also be triggered if validation criteria defined by the method or laboratory are not met, including out-of-trend (OOT) results. To simplify the text, only OOS is used.

The management of OOS results includes:

a. Documented investigation and approval on scientific basis of the decisions taken regarding the acceptance or not of a result.

b. Determination of the cause of the OOS results.

c. Definition of the related corrections and corrective actions.

This Annex presents one approach; other approaches with different steps may be acceptable, as long as they are predefined, scientifically justified and documented.

2. Responsibilities

This Annex applies to results from physicochemical, microbiological and biological tests generated against specification limits given in compendial texts (e.g. Ph. Eur.) or provided by the manufacturer of the tested product.

2.1 Responsibilities of the analyst

The analyst is responsible for carrying out the testing, according to their qualifications and competences, with the required measurement equipment, qualified and/or calibrated in compliance with the procedures in force.

It is recommended that samples and preparations of test solutions be retained until the validity of the results generated is verified or until decided by the supervisor, even if the solutions have expired.

In the event of an OOS report, the analyst has to inform the supervisor/manager as soon as possible, initiating the investigation. In cases where the supervisor/manager is not present, the investigation can be initiated in collaboration with a second analyst.

In the event of an obvious error during the analysis, e.g. spilling of solution, incomplete transfer of a quantity, etc, the analyst interrupts the analysis and documents it without delays, retain all technical records and restarts the analysis with correction of the error. If the error is discovered during the investigation of OOS results, this is reported in the OOS template and analysis is re-done with correction of the error.

2.2 Responsibilities of the supervisor

The supervisor is in charge of carrying out an impartial, rapid and unbiased investigation. This involves deciding on the validity of the testing process and highlighting any errors (laboratory operation, materials, methods or environment).

The investigation must be exhaustive and scientific. It can be based on 5M or on another “Root cause analysis” approach.

3. Definitions

5M:

Manpower, Material, Methods, Mother nature (Environment), Machine (Equipment).

Instrument error:

May result from malfunction of the equipment during an analysis. A device failure, mechanical or electrical, must be documented in the investigation report in order to justify the rejection of results, for example.

Investigation protocol:

Investigation to find the laboratory-assigned causes of an OOS result. The laboratory investigation is carried out by first checking a list of parameters, then with investigative test(s); it brings together all of the data that will allow a decision to be reached on the product(s) impacted.

Out-of-trend result:

Result that does not follow the expected trend when compared to previous results. The result is not necessarily OOS but does not look like a typical data point.

Hypothesis testing:

Testing performed to help confirm or discount a possible root cause, i.e. what might have happened that can be tested. For example, this may include further testing using sample filtration or sonication/extraction, and investigation of potential equipment failures. Multiple hypotheses can be explored. Operation performed during the hypothesis testing, e.g. on a solution prepared during the initial analysis (reinjection, re-dilution, etc.) to support the assessment of the root cause.

Most probable cause:

Scientifically justified determination of the source of the error.

Assigned cause:

An identified reason for obtaining an OOS or aberrant/anomalous result.

Root cause analysis:

Process of identifying all root causes that have or may have resulted in an undesirable condition, situation, nonconformity or failure (ISO 18238:2015)

4. Procedure

The purpose of an OOS investigation is to determine the cause of the OOS result which could be related to the analytical laboratory, other causes or the product itself. It must be noted that the initial result should not to be disregarded until the investigation is concluded and the assigned cause identified.

An investigation shall be thorough, timely, impartial, detailed, documented and based on scientifically sound elements, possibly considering trends in the evaluation of the causes of OOS/OOT results. Examples of how to conduct failure investigation are given in Appendix 1 of this Annex. Examples for managing quantitative and qualitative retesting are given in Annexes 3.2 and 3.3, respectively.

5. Resampling

Items collected from different sampling processing should be uniquely identified in the laboratory and results may be pooled when evaluated for homogeneity.

In specific cases, it may be decided to collect a representative sample of the batch, these include:

- the sample/product is not stable;
- insufficient quantity for retesting;
- possible issues due to delivery or storage of the initial sample.

6. Time limits

The laboratory can decide to define time limits for the execution of the different steps of the investigation. For example, time frames/limits should be defined for when an analyst initiates a laboratory investigation report and informs his/her manager, for closure of an OOS investigation in Phase I from the date of initiation by the laboratory, and for closing a Phase II investigation from the date of initiation of Phase II, etc. (see explanation of Phase I and II in Annex 3.2)

7. List of OOS and periodic monitoring / trending

An OOS list, i.e. all initial OOS results, OOS investigations and all samples confirmed to be OOS, should be available and, if considered meaningful, reported at the Management Review, including status, trends and recurrent root causes.

In the case of repeated causes, specific corrective actions can be considered.

Appendix 1

MODEL TEMPLATE FOR FAILURE INVESTIGATION OF OOS RESULTS

Sample information (name and laboratory code)	
Analytical procedure / Test / Parameter (suspect OOS result)	

Y N/NA		Y N/NA	
General			
	weighing error		inadequate ambient conditions (temperature, moisture, etc.)
	contamination from surfaces or glassware		presence of interfering substances
	other possible reasons for OOS result:		
Samples, Reagents, Solvents & Solutions			
	use of wrong reagents/chemical form		error during filtration
	wrong quality or purity of reagents and solvents		inappropriate storage of samples
	inappropriate storage of reagents, solvents and solutions		carry-over
	solutions or reagents expired		abnormal appearance of samples, reagents solvents or solutions
	reagents not dissolved completely		water of sub-standard quality
Reference Standards			
	wrong reference standard or inadequate quality used		error in weighing, dissolution and dilution
	reference standard expired		inappropriate storage of ref. standard
Dilutions & Pipetting			
	glassware or pipetting device with wrong volume		uncalibrated/leaking piston pipettes
	Uncalibrated/sub-standard glassware		dilution error
	pipettes with broken tip		wrong dilution technique
Method Verification			
	deviations from the specified (authorised) method		values below limit of detection/quantitation
	imprecision of observations/results of sample higher than acceptable (RSD, 95%CI)		blank value ignored
	imprecision of observations/results of reference standard higher than acceptable		system suitability test or assay validity criteria (controls, statistics) missing/failed
	measurement outside linear/validated range		trend of routine method (control chart, comparison with manufacturer in OCABR)
Equipment Verification			
	wrong instrument used		wrong instrument parameters
	instrument calibration missing or criteria not met		computerised system (including software) inappropriate
Calculations			
	calculation error		data transfer error
	formula or factor wrong		inappropriate validation of calculating software

	The reason(s) indicated above invalidate the results
	During this failure investigation, no reason to invalidate the OOS result could be found
Decision on the retest programme:	(e.g. number of replicates, operator, reference material, equipment, methods / parameters)

Technician(s) (Signature, Date)		**Supervisor** (Signature, Date)	