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ANNEX 3 – VERIFICATION OF OOS RESULTS
ANNEX 3.3 VERIFICATION OF OUT-OF-SPECIFICATION RESULTS IN QUALITATIVE TESTING

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VERIFICATION OF OOS RESULTS IN QUALITATIVE TESTING

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1. Introduction

This document is an Annex of the core document "Evaluation and reporting of results", *PA/PH/OMCL (13) 113*, in its current version, and it should be used in combination with it when planning, performing and documenting the assessment of qualitative test results which are suspected to be OOS, as well as reporting these same results.

When a suspected OOS test result indicates that a sample is non-conforming, i.e. it does not meet regulatory specifications, it is necessary to decide whether a retest of that sample is appropriate. Therefore, this document should be considered as guidance for OMCLs and should not be taken as a list of compulsory requirements. It is left to the professional judgement and background experience of each OMCL to decide on the most appropriate procedures to be undertaken in order to demonstrate that the evaluation and reporting of results has been well managed.

Special care should be taken with the documentation of qualitative OOS results that are visually detected (e.g. TLC, pharmacognosy tests, appearance of the pharmaceutical dosage form). Photographic records or documented confirmation by a second qualified analyst should be considered.

2. Focus of failure investigation

The same basic principles used for failure investigation of quantitative testing results are applicable, which means that if an OOS result is due to an assignable cause (e.g. sample integrity problem, or to a traceable laboratory or operator error), then the results of the initial test may be invalidated and need not be taken into consideration in the final results. If an OOS result is not due to a sample integrity problem, or to a laboratory or operator error, a supervisor with requisite expertise should ascertain whether the OOS result is a valid test result for reporting purposes, or whether it requires further verification via retesting. Moreover, as this process covers qualitative tests, for which the investigation is, in general, simpler, there is no need to distinguish between Phase I and Phase II during the OOS investigation, as established for quantitative tests (Annex 3.2).

For qualitative tests, the focus of failure investigation should be further adapted, in order to help to clarify the following situations:

- In cases of non-detection of specified analytes, the focus should be on:
    - influencing factors for possible analyte degradation (e.g. sample storage)
    - confirmation of sample addition
    - possible loss during extraction/sample preparation
    - detection mechanisms of the equipment used

- In cases of detection of unspecified analytes, the focus should be on possible cross-contamination or carry-over from other samples, reference standards, surfaces, glassware or equipment.

The purpose of this stage is to determine whether the reportable result initially obtained is considered to be valid for reporting purposes, or it requires verification/confirmation via retesting.

It is important to ensure that the full testing procedure is followed, which may include guidance on additional steps to perform if the sample does not comply at the first stage.

For example, the following text for the identification of an active substance by FTIR is commonly found in Ph. Eur. monographs and general chapter *2.2.24*: *If the spectra obtained in the solid state show differences, mix 1 part of the substance to be examined and 1 part of the reference substance separately with 30 parts of anhydrous acetone R and heat to boiling to dissolve. Recrystallise and record new spectra using the residues.* It must be ensured that the full procedure is followed, namely perform re-crystallisation before considering the result as suspect OOS.

In the case of microbiological contamination in a Test for Sterility, the European Pharmacopoeia defines the strict conditions under which a test can be invalidated and a new test performed. There are no definitive guidelines, however, for other qualitative microbiological tests, for example, tests for specified microorganisms.

3. Retest programmes

In cases where the failure investigation casts doubt on the presence of an analyte or the absence of cross-contamination, and if required due to the nature or origin (in terms of documentation or method validation) of the test, a retest programme should be implemented. This programme should include performance of an additional independent determination as a retest to exclude undetected errors, whether using a retained sample or a new sample from the same batch and, where practicable, retesting should be preferably be performed by an analyst not involved in the initial test.

A retest result should not be used to ignore or overrule an initial OOS result if it does not confirm the initial OOS result, unless scientifically justified. When an OOS result is not confirmed, the OMCL should scrutinise the entire testing process to establish the cause of disagreement of results. The OMCL should determine which test results should be reported, or whether both test results (initial and retest results) should be reported. The decision tree is depicted in Figure 1. The rationale for these decisions should be documented.

Unlike for chemical testing, retesting of microbiological samples can be problematic. Microorganisms in the sample are alive. Over time they can increase or decrease in number, or die, as a response to external stimuli. Viable microorganisms might not be distributed homogeneously throughout a test sample. As the portion of sample used in the initial testing is typically not available for retesting (as it was destroyed in the initial test), a further aliquot of the sample for retesting might not be the same as the initial sample tested.

The retesting strategy also depends on the validation status of the test method according to the OMCL Guideline “Validation/verification of analytical procedures” (PA/PH/OMCL (13) 82 current version), and should be addressed accordingly (Figure 1).

3.1. Method published in the European Pharmacopoeia (compendial method) (Table 1)

For analytes that are described in the Ph. Eur. and are analysed according to the respective monograph, in case the failure investigation does not cast any doubt on the reliability of the initial OOS result (no assigned cause) the test has to be repeated using the same Pharmacopoeia

method. If the result of the retest is not in compliance with the specification of the monograph, the OOS is confirmed and the initial result reported.

3.2. Validated method from a manufacturer (Table 2)

According to ICH Q2, it is not always possible to demonstrate that an analytical procedure is specific for a particular analyte (complete discrimination). In this case, a combination of two or more analytical procedures is recommended to achieve the necessary level of discrimination. Therefore, the MAH dossier of an authorised product (approved by the National Competent Authority [NCA]) should include descriptions of second/other identification methods, but in rare cases these are not described. If a retest is applicable, it should be performed with the second/other method(s) as described in the dossier, if available.

If the MAH dossier has been approved without a description of second/other confirmation methods, the laboratory should prepare an adequate retest programme, taking into account all the characteristics of the test in question and the results of the "initial OOS" investigation. If advanced identification techniques, such as MS or NMR, are approved techniques included in the MAH dossier, then retesting may be dismissed. Additional tests and analytical techniques not described in the MAH dossier can be used as a part of the hypothesis verification.

As results will be obtained by different test methods, both duly approved in the MAH dossier, then all the results should be reported in the analytical test report.

In this case, the OMCL or the NCA should discuss the situation with the MAH.

3.3. Other situations

This approach is applicable for the following situations described in the OMCL Guideline Validation/verification of analytical procedures:

- method of one manufacturer used for a product from a second manufacturer (Table 2)
- non-compendial published method (Table 3)
- active substance method used for a medicinal product (Table 4)
- screening for non-compliance (Table 6)
- screening for unknown products/contaminants (Table 7)

The first step of the retest programme should be to use the method described in the MAH dossier and approved by the NCA, followed by any other method(s) as described in the dossier for the respective product, if available, or by a validated internal method suitable for the test.

Alternatively, if the test method implemented at the laboratory is, for instance, identification of an analyte using advanced identification techniques, such as MS or NMR, the nature of the test is self-confirmatory and may not require retesting to be performed.

If the authorised and validated other methods lead to divergent results, the OMCL should perform a critical analysis of the data. Nevertheless, if an authorised MAH method is used, it is legally binding and it supersedes the result of the initial method and the result of the other methods. If necessary, the OMCL or the NCA should discuss the situation with the MAH.

Figure 1 - Decision tree for qualitative methods