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ANNEX 3 – VERIFICATION OF OOS RESULTS
ANNEX 3.2 VERIFICATION OF OUT-OF-SPECIFICATION RESULTS IN QUANTITATIVE TESTING

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VERIFICATION OF OOS RESULTS IN QUANTITATIVE TESTING

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1. Introduction

The investigation includes two phases:

- Phase I: the objective is to identify an assigned cause linked to a laboratory issue or not. If no assigned cause is found, the investigation must continue with Phase II (Figure 1) of this document. For the failure investigation, consult Annex 3.1
- Phase II: describes how results from initial and repeat testing can be evaluated in order to reach a consistent conclusion on the sample (Figure 2).

The Phase II described in this Annex is not applicable to pharmacopoeial tests (dissolution test, uniformity of content, etc.) for which the conditions for repeating the test are given in the compendial text.

It is recommended to identify each OOS investigation.

2. Phase I: Identification of the assigned cause

The aim of Phase I is to investigate possible sources of error(s) in the testing process. This evaluation is carried out collaboratively by the analyst and the supervisor via a documented investigation of the possible sources of laboratory error. The initial result is invalidated if the assigned cause is identified. Otherwise, the investigation should be continued to verify hypotheses of a possible root cause. Sample and standard preparations shall not be discarded during this phase, in order to use the same preparations to test hypotheses regarding laboratory error or instrument malfunction.

2.1 Investigation of possible sources of error

The investigation should be conducted by the analyst and supervisor, using a model template for failure investigation of OOS results (Appendix 1 of Annex 3.1). The aim is to determine whether there has been a obvious error in the process of testing. The following steps should be taken as part of the assessment:

1. Discuss the test method with the analyst/supervisor; confirm analyst knowledge and performance of the correct procedure. During this step check if the method was correctly applied, following the prescribed conditions, using the correct materials, etc.

2. Examine the raw data generated during the analysis (chromatograms, spectra, etc.) and check if there are atypical or suspicious data.
3. Verify that the calculations used to convert raw data values into a final result are scientifically sound, appropriate and correct; also determine if unauthorised or non-validated changes have been made to automated calculation methods.
4. Confirm the performance of the instruments (e.g. check the last level III and IV qualification).
5. Determine that appropriate reference standards, solvents, reagents and other solutions were used and that they meet quality control requirements.
6. Evaluate whether the testing method fulfils the criteria based on method validation/verification and historical data.
7. Fully document and retain records of this laboratory assessment.

The assignment of a cause for OOS results will be greatly facilitated if the retained sample/standard preparations are examined promptly.

It is recommended to take into consideration historical information or trends related to similar products or methods/equipment used which previously gave atypical results.

Where the investigation finds that the result is due to analyst error, it is necessary to consider whether retraining may be necessary.

All evidence (e.g. raw data and records) generated during the investigation are to be documented and retained.

The investigation is concluded either with:

2.1.1 Assigned obvious laboratory cause

If the cause of an OOS result has been identified/assigned, the initial result has to be invalidated and the analysis has to be repeated, starting at the step before the identified cause. Examples:

- Where the cause is related to calculation or transcription error, the analyst has to correct the error and check if the recalculated result is in specification after using the correct formula.
- If the cause is due to equipment malfunction, e.g. related to the injection system, after eliminating the source (e.g. bubbles in injector), re-analyse the same solutions applying the prescribed method conditions, if stability data allows (e.g. re-inject the same vial).

Identified non-conformities are corrected and corresponding corrective actions defined if this is deemed necessary. The results obtained are documented and compared to the acceptance criteria/specification limits. If the results are in compliance with the specification, the Phase I investigation can be closed and the results reported. In this case, since an assigned cause has been found, the results obtained from the repeated analysis replace the initial results.

Otherwise, repeat the analysis from the beginning applying the Initial testing decision tree (Section 4.1.1 of the core document), starting from the preparation of solutions.

2.1.2 Further investigations to verify hypotheses

If an assigned cause is not identified, but hypotheses of possible causes exist, these have to be evaluated/tested.

Hypotheses regarding what might have happened (e.g. dilution error, instrument malfunction) should be tested. Several hypotheses can be tested simultaneously or consequently, according to a defined protocol. As an example, possible causes can be verified by re-analysing the initial standard/sample solutions or the initial sample.

Examples:

- Solutions can be re-injected as part of an investigation where a transient equipment malfunction is suspected. Such hypotheses are difficult to prove. However, reinjection can provide evidence that the problem should be attributed to the instrument, rather than the sample or its preparation.
- If there is a suspicion that the reference standard is not well dissolved, different dissolution times, different solvents or different filters can be tested.
- For non-destructive testing of finished dosage forms (e.g. uniformity of weight), where possible, examination of the original dosage unit tested might allow assessment of whether it was damaged during laboratory handling in a way that affected the results. Such damage would provide evidence for invalidating the OOS test result, and a retest would be indicated.
- Further extraction of a dosage unit, where possible, can be performed to determine whether it was fully extracted during the original analysis. Incomplete extraction could invalidate the test results; furthermore it may lead to questions regarding validation of the test method.

It must be underlined that the objective of these investigations is to determine an assigned laboratory cause by verification of a hypothesis, not to generate results considered valid for testing.

Each hypothesis is tested by pre-defining the objective and conditions. Conclusions regarding the verification of the hypothesis are to be documented.

If the cause of an OOS result is not identified and the hypotheses tested were not conclusive, no assigned cause is found. If the method is used for screening purposes, it is recommended to repeat the analysis applying the manufacturer's method or a duly validated, fit-for-purpose method. Otherwise, Phase II has to be initiated.

3. Phase II: Verification of OOS by retesting

If no laboratory-assigned cause is identified in Phase I of the OOS investigation, the result is confirmed by retesting. Phase II describes the steps to reach a conclusion about compliance of the sample, considering all valid results obtained. The objective of Phase II is to verify the initial OOS by retesting.

3.1 Retest with approved protocol

The first step of Phase II consists in a retest with conditions described in an approved protocol following the steps defined in the Initial testing decision tree (steps 1 to 6) depicted in Fig. 1 of the core document. The objective, the procedure (e.g. number of determinations) and the acceptance criteria of the retest are defined and approved by the laboratory manager. The retest on the initial sample shall be carried out according to the original method applied.

The retest is conducted as a repetition of the initial analysis (i.e. number of independent determinations according to the test method) on the initial sample (except in justified cases, e.g. resampling). Following the principles described in Annex 2, a maximum of 6 independent determinations should be performed.

The "initial result" is the one that triggered the OOS investigation. The relative standard deviation (RSD) of initial and retest results (considering the values of all independent determinations) should be calculated and the consistency of the results should be checked by comparing with the corresponding T2 values in Annex 2. If the reportable results are consistent, Phase II can be closed and the results reported as the mean of the initial and retest results (Example 1).

Where the reportable results are not consistent (Example 2), the lack of consistency should be investigated using Annex 3.1 to address possible causes of inconsistency. Further testing can be conducted for investigative purposes only, with the aim of testing possible hypotheses of lack of consistency between the generated results.

Example 1 (consistent results)

A product has specification limits of 99.0-101.0%. The initial testing has been performed as three independent determinations and the results obtained were 98.821%, 98.423% and 98.622% with an average of 98.622% and an RSD (n=3) of 0.20%. The validity of the initial result has been checked according to the criteria laid down in Annex 2, and the obtained RSD is below the threshold of 0.30% given for n=3. Because the average value is below the lower specification limit, retesting has been carried out and three additional independent determinations have been performed on the same sample. The results obtained were 99.454%, 99.283% and 99.090%, with an average of 99.276% and an RSD (n=3) of 0.18%, which is below the threshold of 0.30% given for n=3. In order to check the consistency of the initial and retest results, the RSD% of all independent determinations was calculated (RSD% (n=6) of 0.40 % was obtained). According to Table 2 in Annex 2, for B = 1%, the RSD should be below 0.61% (T2) for n=6 independent determinations. The results are consistent and they should be reported as the mean of all six results (98.949%). The result should be reported as 98.9% (does not comply with the specification limits).

Example 2 (inconsistent results)

A product has specification limits of 99.0-101.0%. The initial testing has been performed as three independent determinations and the results obtained were 98.821%, 98.423% and 98.622% with an average of 98.622% and an RSD (n=3) of 0.20%. The validity of the initial result has been checked according to the criteria laid down in Annex 2, the obtained RSD is below the target for n=3 of 0.30%. As the average is below the specification limits, retesting has been carried out and three additional independent determinations were performed on the same sample. The results obtained were 99.784%, 99.861% and 99.453%, with an average of 99.699% and an RSD (n=3) of 0.22%, which was found below the target RSD given in Annex 2 of 0.30% for n=3. In order to check the consistency of the initial and retest results, the RSD% of the results from all independent determinations was calculated (an RSD% (n=6) of 0.62 % was obtained). According to Table 2 in Annex 2, for B = 1%, the RSD should be below 0.61% (T2) for n=6 independent determinations. The results are inconsistent and if there is no cause, they should be reported separately: 98.6 % (does not comply with specification limits) and 99.7% (complies with specification limits).

However, if a cause has been found for inconsistency, 3 scenarios are possible:

1) Both initial and retesting results are affected; in such cases both results are considered not valid. A corrective action has to be put in place before re-starting testing from the beginning. Testing should restart following the initial conditions and the Initial testing decision tree.

2) Only the results generated in the initial testing are affected, and are therefore to be considered not valid.

a. If Phase II results are in compliance, the investigation can be closed and Phase II results reported.

b. If Phase II results are not in compliance, the results obtained are to be evaluated using the steps described under Phase I investigation.

3) If only the results generated in Phase II are affected (retesting) this result is not considered valid; therefore retesting should be repeated, putting in place corrective actions if needed, starting with retesting with an approved protocol (first step of Phase II decision tree).

It must be underlined that, unless there is an assignable cause leading to the exclusion of retesting results, the number of retests within the retest phase has to be limited in order to avoid “testing into compliance”.

Figure 1: Phase I decision tree

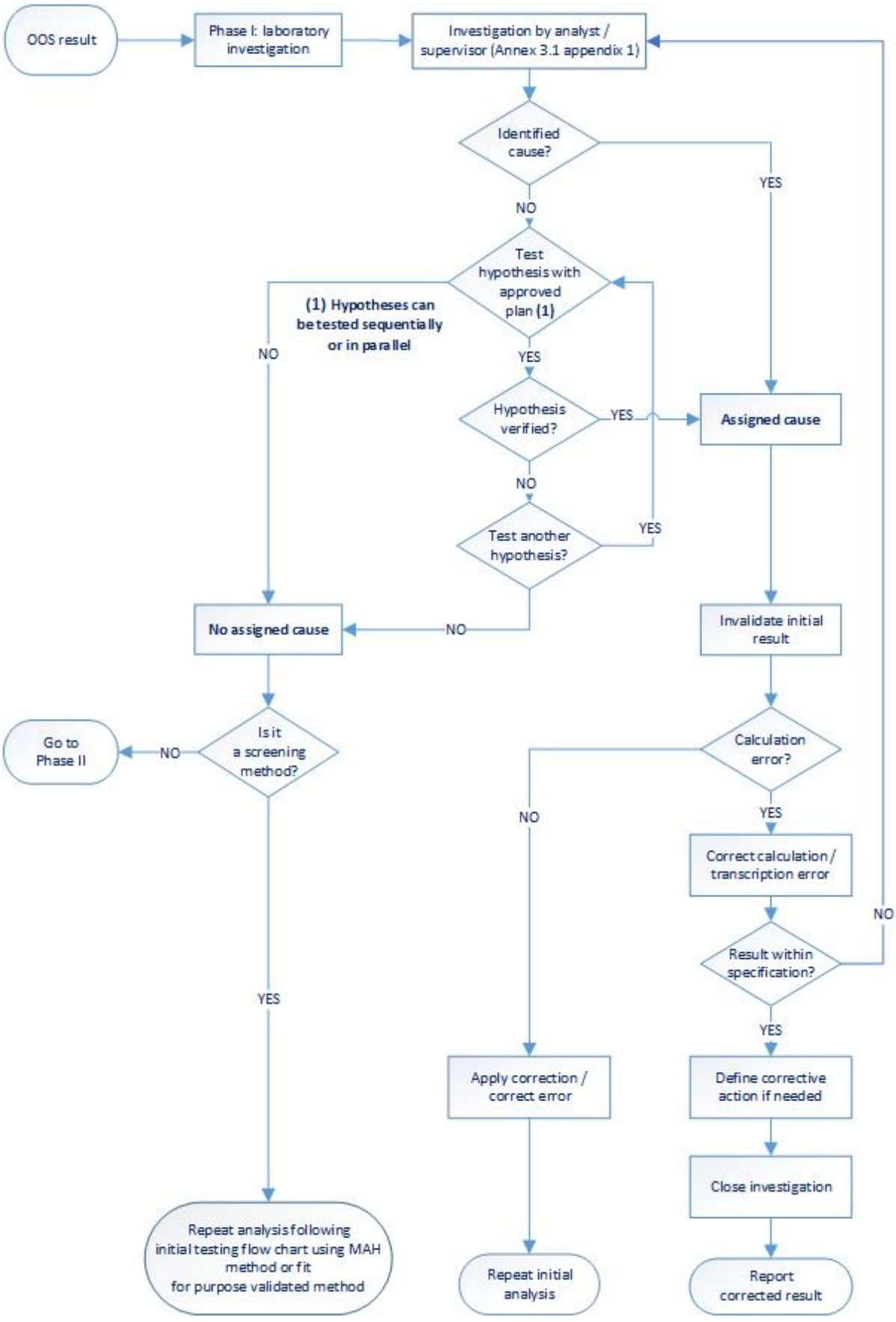

Figure 2: Phase II decision tree