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**Evaluation and Reporting of Results
Core document**

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EVALUATION AND REPORTING OF RESULTS CORE DOCUMENT

GUIDELINE FOR OMCLs

1. SCOPE

This guideline defines basic principles for evaluation and reporting of results of Official Medicines Control Laboratory (OMCL) testing of industrially-manufactured medicinal products¹, extemporaneous products and APIs. The purpose of this OMCL testing is to secure compliance of a product with the specifications laid down in the Marketing Authorisation and other relevant regulations. The OMCL testing can be considered as a verification of the testing by the manufacturer who has declared that the same product is in compliance with the specifications.

In order to simplify the management of the guideline, the present document contains only the general chapters. The annexes can be found in separate documents.

The list of annexes, included in this document, will be updated as soon as new annexes are issued.

2. INTRODUCTION

An OMCL performs testing of medicines for human and veterinary use on behalf of the Competent Authority.

The testing by an OMCL is performed within the context of activities such as market surveillance studies (MSS), testing of centrally authorised products (CAP), testing of products with mutual recognised or decentralised authorisation (MRP/DCP) or national authorisation, official control authority batch release (OCABR) and pre-licensing evaluation. The OMCL should operate the testing within a quality system based on ISO 17025 to guarantee a sufficient level of confidence in the results. The results of the OMCL testing may have significant consequences for the products involved, especially if a sample is found to be out-of-specification (OOS). Measures taken by the Competent Authority may include recalls, batch rejection, thorough production investigations, refusal of marketing authorisation (in pre-licensing evaluation) and it should be noted that results obtained from the testing by OMCLs are communicated within the OMCL Network and to all Competent Authorities.

Therefore, OMCLs have to give careful consideration to the establishment of a test result and any conclusions of conformity or non-conformity of a product.

This document is not necessarily applicable to medicinal products for which a clear specification is missing, as they are neither monographed nor required to go through a complete marketing authorisation procedure (e.g. some European countries define reduced marketing authorisation requirements for herbals for traditional use).

¹ The term “medicinal product” follows the definition of Directive 2004/27/EC, as amended.

3. TEST RESULTS

Test results are to be obtained using validated methods. Guidance on validation of methods by OMCLs is provided in a separate document [1]. Operating conditions have to be followed and analytical acceptance criteria (e.g. system suitability tests) have to be met. All tests are to be performed by competent staff and all results are to be verified and authorised.

A single reportable test result or determination may be calculated from a number of individual observations (e.g. readings or injections). This number has to be predefined in the test protocol.

Uncertainty of measurement. Information on the precision or measurement uncertainty of the results has to be available (preferably by in-house validation according to the OMCLs internal quality control criteria, or by access to the manufacturer's data in the relevant marketing authorisation dossier; see OMCL Guideline "Uncertainty of Measurement" Part 1) and the OMCL has to be able, where appropriate, to report on this issue. Appropriate controls for precision and accuracy must be taken into consideration, where relevant, in the design of the assay.

For all quantitative measurements, the uncertainty of the measurement should be considered in the result. This uncertainty can be expressed as one of the following:

- a. confidence limits with a defined probability (e.g. $P=0.95$), for a defined number of observations.
- b. relative standard deviation, which should not significantly exceed the relative standard deviation established in the method validation.²

For Ph. Eur. monographs, it should be noted that the Ph. Eur. states that no further tolerances are to be applied to the limits prescribed since they are based on data obtained in normal analytical practice and they take account of normal analytical errors, acceptable variations in manufacturing and compounding and deterioration to an extent considered acceptable. This also applies to preparations described in the Ph. Eur.

4. EVALUATION OF RESULTS

In MSS, CAP, MRP/DCP testing and OCABR, the OMCL test results should be assessed against specifications approved in the marketing authorisation and/or the Ph. Eur. monograph of the product concerned.

The OMCL should clearly define how, if applicable, averaging of results is performed and how these results are evaluated.³ The analytical acceptance criteria should comply with

² The use of the relative standard deviation as a global estimation of uncertainty is a simplified approach and, when necessary, the OMCL should take into account other relevant sources of uncertainty, such as calibration and recovery.

³ An average can provide more information about the true value of a product than an individual test result, but it can also hide variability among individual test results.

predefined criteria as described in the documents “OMCL Policy on the Estimation and Application of Uncertainty in Analytical Measurements”.

4.1 FAILURE INVESTIGATION OF OUT-OF-SPECIFICATION (OOS) RESULTS

When a result does not comply with the specifications (“suspected OOS”), the OMCL has to operate a standard procedure to establish whether this result is due to analytical error, the influence of variables unrelated to the product, or whether this result reflects the actual quality of the product tested.

A supervisor or a nominated staff member that was not directly involved in the analysis and who has appropriate competence for the specific analytical technique has to conduct a documented investigation of any suspected OOS result, based on the information provided by the staff that performed the test^{4,5}. If this investigation reveals a technical reason for the suspected OOS result, such as an analyst’s mistake, malfunctioning laboratory equipment, unsuitable reagents/reference substances or inappropriate sample storage, the assay is not valid and the result must be rejected. Non-conformities detected during the failure investigation should be managed according to the quality management system in place, as appropriate. The OMCL must repeat the test and only the result of the repeated test can be considered for evaluation.

The exact cause of an OOS result by the OMCL can often be difficult to identify. After the initial investigation, the OMCL or the Competent Authority that gives the order to test the medicinal product may decide to review information from the manufacturer on the production and control of the suspect batch in the investigation.

4.2 RE-TEST PROGRAMME FOR CONFIRMATION OF OOS RESULTS

If the suspected OOS result cannot be explained by a non-conformity detected during failure investigation, it is considered as “initial OOS result” and the OMCL has to perform a re-test programme to confirm the OOS result. In such cases, the numbers of replicates and operators, sampling procedure and the method for evaluating the results have to be predefined and documented, either by a standard operating procedure or for the individual case. The OMCL may decide on alternative analytical approaches, as long as it is able to demonstrate their validity as confirmatory testing.

If the re-test programme is defined in the Ph. Eur. (e.g. repetition of the rabbit pyrogen test), that re-test programme should be followed. The exact design of the re-test programme, in terms of repeat testing and evaluation of the results, is generally not described in the Marketing Authorisation dossier.

Depending on the type of activity, specific documents may be available that define the different steps of the investigation and actions to be taken in cases where OOS results are

⁴ Annex I.A gives an example of a template for use in the failure investigation of OOS results.

⁵ Annex I.B, FDA “Guidance for Industry - Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production” chapter III.B “Responsibilities of the Laboratory Supervisor” gives information concerning the steps taken as part of the supervisor’s assessment.

obtained (e.g. in the CAP programme, see document “Testing of Centrally Authorised Products (CAPs): Handling of out of specification (OOS) results”).

The re-test programme and its evaluation should be based on sound scientific judgement and may depend on the characteristics of the test. Several examples of approaches for a re-test programme are given in Annexes II A-D. These examples are not mandatory and other approaches are possible if their scientific rationale is documented and the mandatory basic principles of this core document are followed:

- Unless proven to be invalid, the initial OOS result must not be rejected, but has to be included in the evaluation of the product, as for all other valid results.
- All re-tests should be performed independently of each other, including sample preparation.
- The maximum number of re-tests should be predefined and limited and should not be defined so as to “test a product into compliance”. The results should give a basis for the estimation of measurement uncertainty if this is not known from available validation data (preferably in-house, alternatively from the marketing authorisation dossier).

5. REPORTING OF RESULTS

The OMCL should transfer the result and its assessment in a test report to the Competent Authority and, if applicable, to other OMCLs and the EDQM. The information given in the test report must be based on the requirements given in ISO 17025 (Chapter 5.10) and should include all the information requested by the Competent Authority and necessary for the interpretation of the test result, e.g. the relevant specification. The report must make reference to the method used (in-house/compendial/reference material, where relevant). The results should be reported as the mean of all valid results, given with the adequate number of figures and, where appropriate, information on the uncertainty of measurement (e.g. the relative standard deviation or the 95% confidence interval). The OMCL may report the results differently, taking into account internal or customer requirements, as long as they still comply with ISO 17025 (Chapter 5.10).

If a product does not comply with the specification, a critical evaluation based on the OMCL failure investigation procedure has to be given and, if applicable, information from the manufacturer. A recommendation to the Competent Authority for follow-up activities may be included in the report.

However, where specific procedures already exist for the reporting of results (e.g. OCABR – EC Administrative procedure for OCABR), these should be followed and any circulation of information to other organisations should respect the limits of confidentiality characteristic of that activity (e.g. EU-specific networks versus general OMCL activities). In addition, the OMCLs and Competent Authorities involved should define their in-house procedures for storage and internal exchange of data and any follow-up measures, taking into account the recommendations described above.

6. GLOSSARY

API	Active Pharmaceutical Ingredient
CAP	Centrally Authorised Product
MRP/DCP	Mutual Recognition Procedure / Decentralised Procedure
MSS	Market Surveillance Study
OCABR	Official Control Authority Batch Release
OOS	Out of Specification

7. REFERENCES

(For all references, the latest version applies)

- 1 OMCL Guideline “Validation of Analytical Procedures” (PA/PH/OMCL (05) 47 DEF).
- 2 OMCL Guideline “Uncertainty of Measurement Part 1 - General OMCL Policy for Implementation of Measurement Uncertainty in Compliance Testing” (PA/PH/OMCL (05) 49 DEF CORR).
- 3 FDA “Guidance for Industry - Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production”
- 4 EN ISO/IEC 17025 General Requirements for the Competence of Testing and Calibration Laboratories

8. ANNEXES

The annexes of this Guideline contain several examples of approaches to failure investigation and the re-test programme. Other approaches are possible if their scientific rationale is documented and the basic principles of this core document are followed.

I FAILURE INVESTIGATION OF INITIAL OOS RESULTS

I A Model Template for failure investigation of OOS results

I B FDA “Guidance for Industry - Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production” chapter III.B “Responsibilities of the Laboratory Supervisor” (Annex I.B, for consultation).

II EXAMPLES FOR RE-TEST PROGRAMMES

II A Re-test programmes for quantitative tests

*II B Calculating tool for Annex II A – **FOR INTERNAL USE ONLY; NOT INCLUDED IN THE PUBLISHED PACKAGE***

II C Re-test programmes for qualitative tests

II D Special considerations for animal testing