European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

Funded by the European Union and the Council of Europe

EUROPEAN UNION

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Implemented by the Council of Europe

General European OMCL Network (GEON)
QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (13) 82 R5

Validation/Verification of Analytical Procedures

Full document title and reference	Validation/Verification of Analytical Procedures *PA/PH/OMCL (13) 82 R5*
Document type	Guideline
Legislative basis	Council Directive 2001/83/EC and 2001/82/EC, as amended
Date of first adoption	October 1999
Date of original entry into force	February 2000
Date of entry into force of revised document	July 2020
Previous titles/other references / last valid version	Last adopted version *PA/PH/OMCL (13) 82 2R*
Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
Concerned Network	GEON

N.B. This OMCL Quality Management System document is applicable to members of the European OMCL Network only. Other laboratories might use the document on a voluntary basis. However, please note that the EDQM cannot treat any questions related to the application of the documents submitted by laboratories other than the OMCLs of the Network.

Note: Mandatory requirements in this guideline are defined using the terms "shall" or "must". The use of "should" indicates a recommendation. For these parts of the text otherappropriately justified approaches are acceptable. The term "can" indicates a possibility or an example with non-binding character.

INTRODUCTION

The ICH Guideline on "Validation of Analytical Procedures: Text and Methodology" (Q2) constitute a discussion of the validation characteristics that should be considered during the validation of an analytical procedure (the guideline has also been adopted for veterinary products during VICH discussion). They are primarily addressed to pharmaceutical industry indicating which validation data need to be provided in an application file. These data should demonstrate that the proposed testing and acceptance criteria are sufficiently under control to guarantee reproducible quality of the products at release and adequate control during shelf-life (stability).

As the circumstances under which an OMCL works are different from those of a pharmaceutical company – in most cases no routine analysis, but often responses to be made in a short period of time - the extent of analytical validation/verification requested before performing an analysis needs to be reconsidered. On the other hand, it has in all cases to be guaranteed that the result submitted is reliable. It should also be emphasised here, that adequate reference materials are an important factor in both the performance of the validation/verification studies and the analysis itself. The use of widely accepted reference preparations can in certain circumstances avoid the consideration of some validation characteristics, mainly in the field of biological products: this has then to be justified on a case by case basis. The OMCL may decide the extent required considering the risk factors.

The scope of this document – specifically addressed to OMCLs - is to give guidance on the extent of validation/verification needed, depending on various circumstances i.e. objective of the analysis (e.g. screening for non-compliance), amount of validation data already available (e.g. in case of a method transfer), experience or historical data already available in the individual OMCL (e.g. recovery from a complex matrix; routine use of a standard titration even if different substances are titrated), etc. This document is equally applicable to products of synthetic and of biological origin. It does not address common laboratory practice: for instance guidance concerning the use of the equipment, calibration etc.

This document is a note for guidance, which provides detailed recommendations of the extent of the validation/verification exercise dependent on the category of the analytical procedure; it should be noted that other approaches are always possible. With respect to the new Directive 2010/63/EU on ethical animal use for scientific and educational purposes and the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Council of Europe) special attention is needed for the use of *in vivo* methods as analytical procedures. All efforts should be made to rationalise and restrict animal use to a necessary minimum based on a thorough analysis of the situation. It should be stressed that this document cannot provide detailed advice for all possible cases where *in vivo* tests are used. The purpose of this document is to provide general guidance.

In all cases a short description and/or justification of the approach chosen, including the methods, should be described in the internal documentation of the analysis. Validation data

of validated methods (compendial, marketing authorisation dossier) should be available. Modifications from the original validated method shall be justified. Depending on the nature of the modifications and the outcome of the risk assessment, supplementary validation or verification activities may be undertaken.

The same definitions as in the ICH document apply.

CATEGORIES OF ANALYSIS

This chapter defines the different analytical situations (categories) which might occur in an OMCL and the corresponding validation characteristics which should be considered. Refer to the current version of the ICH guideline on "Validation of Analytical Procedures: Text and Methodology" (Q2).

Formal validation studies, according to the ICH requirements, must be performed for a new developed method or when for an existing method the validation data must be completed. According to ISO 17025, validation is required for non-standard methods. In the OMCL context, pharmacopoeial methods and validated methods from a Marketing Authorisation are considered to be standard methods.

Verification of Method must be done to show that under actual conditions of use in the individual laboratories the (validated) method is adequate (fit for use). This may be achieved by carrying out the system suitability tests (e.g. resolution in a chromatographic method), controlling sensitivity at the reporting threshold, controlling the completeness of a reaction step (e.g. extraction, hydrolysis reaction) before the actual determination can be performed, verifying the precision of the method etc. This may also be achieved by carrying out a method transfer exercise, in the laboratory that has established the method and the OMCL and the results compared to show equivalence.

In all cases, a short note, explaining the rationale for the chosen approach - depending on the complexity of the analysis required -, should be provided in the internal documentation of the analysis. Deviation from this guideline shall be justified.

Several categories of analysis are considered in Tables 1 – 8:

Table 1: Method published in the European Pharmacopoeia

Analytical procedures described in a monograph are considered validated. The OMCL must verify that all reference materials needed are available and the required system suitability tests are performed. For related substances tests, specificity for any known impurities not listed in the monograph (e.g. Ph Eur transparency list) should be verified.
For finished product monographs, the OMCL should verify that any excipients do not interfere in the analysis of the active substance, unless addressed in the monograph.

Note: To fall under this category, the procedures must be described in detail, not for instance as in some cases for biologicals where there is only a general description of the method. The details may come from the published report of the collaborative study (e.g. BSP study reports in Pharmeuropa Bio & Scientific notes)

Test Samples	Method	Checks required by the OMCL
Active Substance	Identification	No formal validation required
	Related Substances	No formal validation required
	Assay	No formal validation required
Medicinal Product	Identification	No formal validation required
	Related Substances	Specificity: no interference from excipients; Reporting threshold (at least the quantitation limit)
	Assay	Specificity Accuracy: mainly recovery, minimum 1 determination. Precision (repeatability): around the target test concentration (minimum 2 independent determinations) Linearity at three measuring points in the range around the target value.

Table 2: Validated method from a Manufacturer (1st MAH)

Analytical procedures taken from a marketing authorisation are fully validated by the company.

Test Samples	Method	Checks required by the OMCL
1st MAH Active Substance	Any	No formal validation required
1st MAH Medicinal Product	Any	No formal validation required
2nd MAH Active Substance	Identification	No formal validation required
	Related Substances	Specificity (impurity profile) (if the impurity profile is different, further validation data might be necessary)
	Assay	No formal validation required in case of a titration Stability indicating: see testing for related substances
2nd MAH Medicinal Product Comparable formulations (matrix) If matrices identical, see 1st MAH Product above)	Identification	No formal validation required
	Related Substances	Specificity (interference of excipients) Reporting threshold (quantitation limit) Precision over range
	Assay	Specificity: no interference from excipients Accuracy: around the target concentration Repeatability: around the target concentration (minimum 2 independent determinations) Linearity at three measuring points in the range around the target value.

1st MAH = product made by the MAH who validated the original method used. 2nd MAH = a product made by a different manufacturer for which the original method used has not been specifically validated

Where methods are from old application file(s) with no or insufficient validation data, the supervising Competent Authority should be informed. For the validation characteristics to be considered see Tables 2, 5.

Table 3: Non-compendial published method

The validation characteristics to be considered will always depend on the amount of validation data provided. If the method has been fully validated and data published in the literature, then see Table 1. If not, the following should be considered

Test Samples	Method	Checks required by the OMCL
Active Substance	Identification	No formal validation required
	Related Substances	Specificity (impurity profile) Reporting threshold (quantitation limit) Precision over range
	Assay	Specificity Accuracy: around the target concentration Repeatability: around the target concentration (minimum 2 independent determinations) Linearity at three measuring points in the range around the target value.
Medicinal Product	Identification	No formal validation required
	Related Substances	Specificity (interference of excipients) Reporting threshold (quantitation limit) Precision over range
	Assay	Specificity: no interference from excipients Accuracy: around the target concentration Repeatability: around the target concentration (minimum 2 independent determinations) Linearity at three measuring points in the range around the target value.

Table 4: Active Substance method used for a Medicinal Product

The main factor to be considered here is the influence of the matrix on the analysis including interference from the excipients.

Test Samples	Method	Checks required by the OMCL
Medicinal Product	Identification	No formal validation required
	Related Substances	Specificity (interference of excipients) Reporting threshold (quantitation limit) Precision: over the range Accuracy: over the range
	Assay	Specificity: no interference from excipients Accuracy: around the target concentration Repeatability: around the target concentration (minimum 2 independent determinations) Linearity at three measuring points in the range around the target value.

Table 5: Methods validated to reduce, refine or replace animal use (3Rs)

Test Samples	Method	Checks required by the OMCL
Active Substance Medicinal Product	Any	In these cases, the verification will generally involve methods validated through collaborative trials, validated by the manufacturer for a particular product, or validated and published by another laboratory. The validation characteristics to be considered will always depend on the amount of validation data provided. If the method has been fully validated and data is published in the literature or available in the MA dossier, then Table 1 applies (active substance and medicinal product). Elements highlighted in Table 2 may also be relevant in these situations. The OMCL should identify the key parameter(s) which should ensure the precision of the test procedure. Wherever possible the same protocols and reference material should be used in all labs. When a laboratory participated in a collaborative study to develop a method, data generated during the study can also be used in the validation package for regular lab use.

Table 6: Screening for non-compliance

Screening for non-compliance means that the target of the analysis is to detect potential non-compliance of the product with the specifications. This type of screening would be performed when a rapid analysis is requested and/or when no validation data of the method are available. The procedure must in all cases be documented.

If non-compliance is detected, the extent of validation must be expanded, for example by considering to switch to a well-recognised method (compendial method or MAH dossier method).

Test Samples	Method	Checks required by the OMCL
Medicinal Product	Identification	Specificity
	Testing for Related substances	Specificity Reporting threshold (quantification limit) Precision over range
	Assay	Specificity: no interference from excipients and related substances Precision: around the target test concentration (minimum 2 independent determinations)

Table 7: Screening for unknown product/contaminants

In these cases, there is a lack of information on the product which must be tested with respect to its label claim (presence or absence of certain substances) or to clarify other aspects asked by the Inspectorate.
Testing to be considered: identification, assay and perhaps purity testing. The first important step is to identify the major components of the product.

Test Samples	Method	Checks required by the OMCL
Active Substance	Identification	Specificity
	Assay	Specificity Linearity at three measuring points in the range around the determined value. Repeatability: around the determined concentration (minimum 2 independent determinations)
	Contaminants	Specificity, detection limit and quantitation limit.
Medicinal Product	Identification	Specificity
	Assay	Specificity: no interference from excipients Accuracy: around the target concentration Repeatability: around the target concentration (minimum 2 independent determinations)
	Contaminants	Specificity, detection limit and quantitation limit.

Table 8: Development of a new method

This is mainly the case where a product is tested in routine testing conditions and/or where an in-house analytical procedure is used.

Test Samples	Method	Checks required by the OMCL
Active Substance Medicinal Product	Any	The analytical procedures should be validated according to the ICH guideline. When tests involve animals, the advice provided by Ph. Eur., ECVAM and EMA on the reduction of animals used in validation of new procedures/test methods should be used, wherever available. Validation of the new assay should not require (re)validation of an established *in vivo* test, even if the original test is not validated according to current validation procedures. Use may be made of any data already available (own/other lab(s) and/or literature).