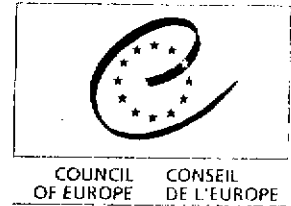


**EUROPEAN DIRECTORATE FOR THE
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VALIDATION OF ANALYTICAL PROCEDURES

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VALIDATION OF ANALYTICAL PROCEDURES

GUIDELINE FOR OMCLs

INTRODUCTION

The two ICH Guidelines on “Validation of Analytical Procedures: “Definition/ Terminology and Methodology” (Q2A and Q2B) 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 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 studies and the analysis it-self. 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 scope of this document – specifically addressed to OMCLs - is to give guidance on the extent of validation 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 specific use of the equipment, calibration etc.

This document is a note for guidance, which provides detailed recommendations of the extent of the validation exercise dependent on the category of the analytical procedure; it should be noted that other approaches are always possible. 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 should be justified. 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. (As a reminder the table in the annex describes in general the validation characteristics to be considered, depending on the different types of analytical procedures).

Formal validation studies, according to the ICH requirements, has to be performed for a new developed method or when for an existing method the validation data have to be completed. Method transfer check (verification of suitability) has to be done to show that under actual conditions of use in the individual laboratories the method is adequate (fit for use). This might imply for instance the carrying out of the system suitability tests (e.g. resolution in a chromatographic method), the control of the reporting threshold, the control of the completeness of a reaction step (e.g. extraction, hydrolysis reaction) before the actual determination can be performed, the verification of the precision of the method etc. So for instance the system suitability tests described in a fully validated liquid chromatography method will in all cases have to be performed, as these tests are part of the analytical procedure. This is particular true for the category 'Transfer of a method'.

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

The following categories of analysis are considered:

- Transfer of a method
- Screening
- Development of a new analytical procedure

1. Transfer of a Method

In this category it is assumed that a certain amount or elements of validation data for this particular analysis is already available: so no or only a few validation characteristics need to be considered. In an ideal situation, this can also be done by comparison of the results of two laboratories performed on the same sample. "No formal validation required" indicates that the respective validation characteristics have already been considered by others. However a verification of suitability under conditions of use (=method transfer check) has to be done in all cases by the OMCL.

1.1. Pharmacopoeial (compendial) method.

1.1.1 Active substance

The analytical procedures described in a monograph of a pharmacopoeia are considered to be validated. In this case it should be made sure that all reference materials needed are available and the required system suitability tests are performed. Nevertheless, it should also be considered that a

pharmacopoeial monograph is only considered validated (related substances test) when it is applicable to the control of the listed impurities (specific source material, see Ph Eur).

Identification:
no formal validation required;

Testing for Impurities:
no formal validation required;

Assay:
no formal validation required.

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.

1.1.2 Medicinal product

The pharmacopoeial monograph for a specific dosage form is a good basis for the analysis; however as in many cases there is no indication about the exact composition of the product (qualitative and quantitative composition of the excipients), it must at least be made sure that these do not interfere in the analysis of the active substance, unless addressed in the monograph.

- Identification:
no formal validation required;
- Testing for Impurities:
specificity: no interference from excipients;
reporting threshold (at least the quant.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.

1.2 Method of a manufacturer.

1.2.1: the analytical procedures have been fully validated by the company.

The same as under A.1.1. applies for both the active substance and the medicinal product:

Identification:
no formal validation required;

Testing for Impurities:
no formal validation required

Assay:
no formal validation required

1.2.2: old application file with no or insufficient validation data published.

This case should be notified to the authorities. For the validation characteristics to be considered please refer to 1.4, 1.5, 2.1 or 3.

1.3 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, the same as under 1.1 applies (active substance and medicinal product). If not, the following has to be considered:

Identification:

no formal validation required

Testing for Impurities:

specificity;
reporting threshold (limit of quantitation);
precision/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.

1.4 Method of a first manufacturer to be used for a product of a 2nd manufacturer.

1.4.1 Active substance:

Identification:

no formal validation required

Testing for Impurities:

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 impurities.

1.4.2 Medicinal product:

A prerequisite is, that we have here comparable formulations (matrix):

Identification:

no formal validation required

Testing for Impurities:

Specificity (interference of excipients);
 reporting threshold (quantit. limit);
 precision/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.

If the matrixes are identical see 1.2.1.

1.5 Method for an active substance to be 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.

Identification:

no formal validation required

Testing for Impurities:

specificity;
 reporting threshold (quantit. limit);
 precision/accuracy over the range .

Assay:

-specificity: no interference from impurities and 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.

2. Screening**2.1. 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 at disposal. The procedure must in all cases be documented.

Minimum validation required:

Identification:

specificity

Testing for Impurities:

specificity;
reporting threshold (quantit. limit);
precision over the range .

Assay: -specificity: no interference from excipients and impurities;
-precision: around the target test concentration, (minimum 2 independent determinations)

If non-compliance is detected or suspected, the extent of validation has to be expanded. The follow-up of possible OOS situation has to be regulated by a standard operation procedure.

2.2. Analysis of an unknown product

In this case there is a lack of information on the product which has to 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.

Identification: Specificity

Assay: -specificity: no interference from the matrix
-accuracy: around the target test concentration, mainly recovery (performed on 2 independent determinations)
-precision: around the target test concentration, (performed on 2 independent determinations)

2.3. Screening for contaminants / Analytical procedures for trace analysis

Mainly the situations as under 1 (transfer of a method) can be encountered; the most important validation characteristics which need to be considered are of course specificity, detection limit and quantitation limit.

3. Development of a new analytical procedure

This is mainly the case where a product is tested in routine testing conditions and/or where an in-house analytical procedure is used. The analytical procedures should be validated according to the ICH guideline.

APPENDIX I

TABLE

Type of analytical procedure characteristics	IDENTIFICATION	TESTING FOR IMPURITIES		ASSAY - dissolution (measurement only) - content/potency	TRACE ANALYSIS
		quantitat.	limit		
Accuracy	-	+	-	+	+
Precision					
Repeatability	-	+	-	+	+
Interm. Precision	-	+(1)	-	+(1)	+
Specificity (2)	+	+	+	+	+
Detection Limit	-	-(3)	+	-	+
Quantitation Limit	-	+	-	-	+
Linearity	-	+	-	+	+
Range	-	+	-	+	+

- signifies that this characteristic is not normally evaluated

+ signifies that this characteristic is normally evaluated

- (1) In cases where reproducibility (see glossary in the ICH guideline) has been performed, intermediate precision is not needed.
- (2) Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).
- (3) May be needed in some cases.

