

# **Guideline for Industry**

## **Text on Validation of Analytical Procedures**

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# GUIDELINE FOR INDUSTRY<sup>1</sup>

## TEXT ON VALIDATION OF ANALYTICAL PROCEDURES

### I. INTRODUCTION

This document presents a discussion of the characteristics for consideration during the validation of the analytical procedures included as part of registration applications submitted within the European Union, Japan and the United States. This document does not necessarily seek to cover the testing that may be required for registration in, or export to, other areas of the world. Furthermore, this text presentation serves as a collection of terms, and their definitions, and is not intended to provide direction on how to accomplish validation. These terms and definitions are meant to bridge the differences that often exist between various compendia and regulators of the European Union, Japan and the United States.

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. A tabular summation of the characteristics applicable to identification, control of impurities and assay procedures is included. Other analytical procedures may be considered in future additions to

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<sup>1</sup>This guideline was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, October 27, 1994. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA. This guideline was published in the Federal Register on March 1, 1995 (60 FR 11260) and is applicable to drug and biological products. In the past, guidelines have generally been issued under § 10.90(b) [21 CFR 10.90(b)], which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but that are acceptable to FDA. The agency is now in the process of revising §10.90(b). Therefore, this guideline is not being issued under the authority of §10.90(b), and it does not create or confer any rights, privileges or benefits for or on any person, nor does it operate to bind FDA in any way. For additional copies of this guideline contact the Consumer Affairs Branch (formerly the Executive Secretariat Staff), HFD-210, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD, 20855, 301-594-1012. An electronic version of this guideline is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

this document.

## **II. TYPES OF ANALYTICAL PROCEDURES TO BE VALIDATED**

The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures:

- Identification tests.
- Quantitative tests for impurities' content.
- Limit tests for the control of impurities.
- Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product.

Although there are many other analytical procedures, such as dissolution testing for drug products or particle size determination for drug substance, these have not been addressed in the initial text on validation of analytical procedures. Validation of these additional analytical procedures is equally important to those listed herein and may be addressed in subsequent documents.

A brief description of the types of tests considered in this document is provided below.

- Identification tests are intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc.) to that of a reference standard.
- Testing for impurities can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test.
- Assay procedures are intended to measure the analyte present in a given sample. In the context of this document, the assay represents a quantitative measurement of the major component(s) in the drug substance. For the drug product, similar validation characteristics also apply when assaying for the active or other selected component(s). The same validation characteristics may also apply to assays associated with other analytical procedures (e.g., dissolution).

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which need to be evaluated. Typical validation characteristics which should be considered are listed below:

- Accuracy
- Precision
  - Repeatability
  - Intermediate Precision
- Specificity
- Detection Limit
- Quantitation Limit
- Linearity
- Range

Each of these validation characteristics is defined in the attached Glossary. The table lists those validation characteristics regarded as the most important for the validation of different types of analytical procedures. This list should be considered typical for the analytical procedures cited but occasional exceptions should be dealt with on a case-by-case basis. It should be noted that robustness is not listed in the table but should be considered at an appropriate stage in the development of the analytical procedure.

Furthermore revalidation may be necessary in the following circumstances:

- Changes in the synthesis of the drug substance;
- Changes in the composition of the finished product;
- Changes in the analytical procedure;

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well.

TABLE

TYPE OF ANALYTICAL PROCEDURE; CHARACTERISTICS	IDENTIFICATION	TESTING FOR IMPURITIES		ASSAY; dissolution (measurement only); content/potency
		Quantitation	Limit	
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Intermediate Precision	-	+ <sup>1</sup>	-	+ <sup>1</sup>
Specificity <sup>2</sup>	+	+	+	+
Detection Limit	-	- <sup>3</sup>	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

NOTE: - signifies that this characteristic is not normally evaluated; + signifies that this characteristic is normally evaluated.

<sup>1</sup> In cases where reproducibility (see Glossary) has been performed, intermediate precision is not needed.

<sup>2</sup> Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).

<sup>3</sup> May be needed in some cases.

**GLOSSARY****1. ANALYTICAL PROCEDURE**

The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

**2. SPECIFICITY**

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc.

Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).

This definition has the following implications:

Identification: To ensure the identity of an analyte.

Purity Tests: To ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e., related substances test, heavy metals, residual solvents content, etc.

Assay (content or potency):

To provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample.

**3. ACCURACY**

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

This is sometimes termed trueness.

#### **4. PRECISION**

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution.

The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

##### **a. Repeatability**

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision

##### **b. Intermediate precision**

Intermediate precision expresses within laboratories variations: different days different analysts, different equipment, etc.

##### **c. Reproducibility**

Reproducibility expresses the precision between laboratories (collaborative studies usually applied to standardization of methodology).

#### **5. DETECTION LIMIT**

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

#### **6. QUANTITATION LIMIT**

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly

for the determination of impurities and/or degradation products.

**7. LINEARITY**

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

**8. RANGE**

The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

**9. ROBUSTNESS**

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.