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Cosmetics — Analytical methods — Development of a global approach for validation of quantitative analytical methods

Cosmétiques — Méthodes analytiques — Développement d'une approche globale pour la validation des méthodes analytiques quantitatives

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Contents

Page

Foreword

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This document was prepared by Technical Committee ISO/TC 217, *Cosmetics*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

The purpose of this document is to propose a characterization protocol for the validation of a quantitative analysis method in the cosmetic field and thus responds to the requirements of ISO/IEC 17025, i.e. using the performance goals as a basis. The theoretical principles of this approach can be found in Reference [1]. This document is based on the French Standard NF V 03-110[2].

Analytical methods for analyses of cosmetics need to be validated. Validation has been long considered as a process consisting in individually verifying several different criteria, i.e. selectivity, repeatability, linearity, trueness, etc. The global approach, as proposed since 2003[1], is based on the total error concept and the term ''global" means that only a single criterion should be checked to validate a method: the agreement between a future experimental result and the true value. This approach has already been applied in the domains of pharmacy[1],[9], agricultural chemistry[2], and is in agreement with quality assurance guidelines such as GLP or ISO/IEC 17025. This validation process applies generally to already developed methods and includes evaluations of the following criteria: specificity/selectivity, precision, trueness, linearity range, LOD/LOQ, stability, ruggedness.

The large number of cosmetic products and the variety of matrices present a challenge for an analytical laboratory requiring that standardized methods to be adapted for each type of samples. Additional difficulties are linked to the very low concentrations to be measured, generally of the order of the mg/kg (ppm) or µg/kg (ppb). In such context, criteria such as accuracy and uncertainty of measurement of the analytical results are of utmost importance.

When the concentration of a substance is determined by an analytical laboratory, it is important to evaluate the gap between the measured value and the known true value. This difference indicates the trueness of the analysis. If cosmetic samples are analysed several times in different conditions (laboratory, instrument, operator), the individual results will present a dispersal around the average value which represents the precision of the measurement. As for the individual measurement, it represents an error with the average value and an inaccuracy with regard to the reference value (i.e. the true value).

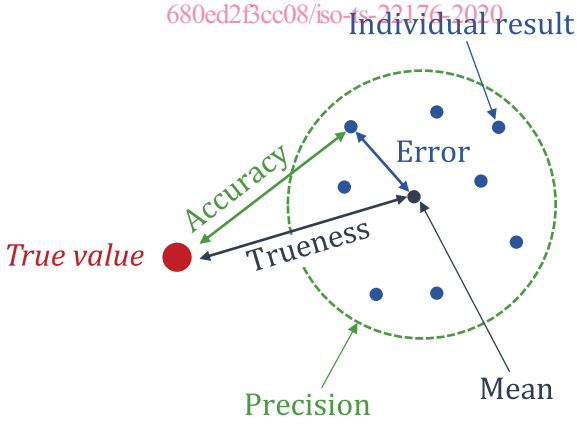
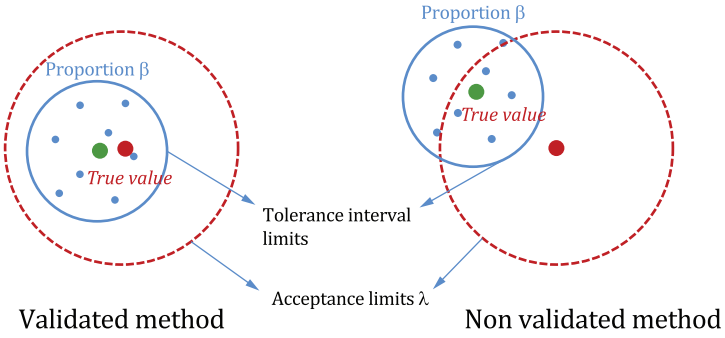


Figure 1 — Illustration of the concepts of accuracy, precision and trueness

When a laboratory measures the concentration of a given substance in a cosmetic product sample, the value which is obtained is thus characterized by a given accuracy which includes at the same time the notion of trueness and precision (see Figure 1). It can also be considered as total error. The insurance that the accuracy of a result is below acceptable limits, is thus one of the ways to make sure of the validity of a measurement.

The accuracy profile (plot of accuracy versus concentration), such as it is developed in numerous domains[3] to [9], is thus the way to know the accuracy on a result obtained with a given method applied to a type of sample in the environment of a given laboratory.

To reach this accuracy profile, it is necessary to undergo a specific assay allowing to demonstrate the validity of the analytical method, as well as the accuracy of the measurement for a given substance. In this approach, it is necessary to determine a tolerance interval[10] which contains a given proportion (β) of future measured values inside (in average). If this tolerance interval is located inside a limit of acceptability defined a priori, taking into consideration several parameters such as the type and concentration of analyte, type of matrix, of analysis and conditions of the experiments, in this case, the method will be considered as valid, and if it goes outside this limit of acceptability, the method will be considered as non-valid (see Figure 2).



Key

- mean value
- true value

Figure 2 — Illustration of the validation principle

Cosmetics — Analytical methods — Development of a global approach for validation of quantitative analytical methods

1 Scope

This document defines a global approach for the validation of a quantitative analytical method, based on the construction and interpretation of an accuracy profile, and specifies its characterization procedure.

This procedure is particularly applicable for internal validation in a cosmetic testing laboratory, but its scope can be extended to the interpretation of data collected for an interlaboratory study designed according to the recommendations of the ISO 5725-1. It does not apply to microbiological trials. The present approach is particularly suited to handle the wide diversity of matrices in cosmetics. This document only applies to already fully-developed and finalized methods for which selectivity/specificity have already been studied and the scope of the method to be validated has already been defined, in terms of matrix types and measurand (for example analyte) concentrations.

2 Normative references

The following document is referred to in the text in such a way that some or all of its content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO/IEC Guide 99:2007, *International vocabulary of metrology — Basic and general concepts and associated terms (VIM)*

3 Terms, definitions and symbols

3.1 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO/IEC Guide 99 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1.1
measurement
process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity

[SOURCE: ISO/IEC Guide 99:2007, 2.1, modified — Notes to entry have been excluded.]

3.1.2
measurand
quantity intended to be measured

Note 1 to entry: The term “analyte”, employed in chemistry, is a synonym of measurand, and is used more generally.

[SOURCE: ISO/IEC Guide 99:2007, 2.3, modified — Original notes to entry have been excluded and a new note to entry has been added.]

3.1.3
measurement trueness
trueness
closeness of agreement between the average of values obtained by replicate measurements of the same or similar objects under specified conditions and a reference quantity value

[SOURCE: ISO/IEC Guide 99:2007, 2.14, modified — Notes to entry have been excluded.]

3.1.4
measurement precision
precision
closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions

[SOURCE: ISO/IEC Guide 99:2007, 2.15, modified — Notes to entry have been excluded.]

3.1.5
repeatability condition
condition of measurement, out of a set of conditions that includes the same measurement procedure, same operator, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time

[SOURCE: ISO/IEC Guide 99:2007, 2.20, modified — Notes to entry have been excluded.]

3.1.6
measurement repeatability
repeatability
measurement precision under a set of *repeatability conditions* (3.1.5) of measurement

[SOURCE: ISO/IEC Guide 99:2007, 2.21]

3.1.7
intermediate precision condition
condition of measurement, out of a set of conditions that includes the same measurement procedure, same location, and replicate measurements on the same or similar objects over an extended period of time, but may include other conditions involving changes

[SOURCE: ISO/IEC Guide 99:2007, 2.22, modified — Notes to entry have been excluded.]

3.1.8
intermediate measurement precision
intermediate precision
measurement precision under a set of *intermediate precision conditions* (3.1.7) of measurement

[SOURCE: ISO/IEC Guide 99:2007, 2.23, modified — Notes to entry have been excluded.]

3.1.9
reproducibility condition of measurement
reproducibility condition
condition of measurement, out of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects

[SOURCE: ISO/IEC Guide 99:2007, 2.24, modified — Note to entry has been excluded.]

3.1.10
measurement reproducibility
reproducibility
measurement precision under *reproducibility conditions of measurement* (3.1.9)

[SOURCE: ISO/IEC Guide 99:2007, 2.25, modified — Note to entry has been excluded.]

3.1.11
measurement accuracy
accuracy
closeness of agreement between a measured quantity value and a true quantity value of a measurand

[SOURCE: ISO/IEC Guide 99:2007, 2.13, modified — Notes to entry have been excluded.]

3.1.12
verification
provision of objective evidence that a given item fulfils specified requirements, taking into account any measurement uncertainty

[SOURCE: ISO/IEC Guide 99:2007, 2.44, modified — Notes to entry have been excluded.]

3.1.13
validation
verification, where the specified requirements are adequate for an intended use

Note 1 to entry: The term "characterization" applies to the method, whereas the term "verification" applies to the outcomes. Validation of the method therefore consists of checking if the results are adequate for an intended use.

[SOURCE: ISO/IEC Guide 99:2007, 2.45, modified — Example has been excluded and a Note to entry has been added.]

3.1.14
selectivity
property of a measuring system, used with a specified measurement procedure, whereby it provides measured quantity values for one or more measurands such that the values of each measurand are independent of other measurands or other quantities in the measuring system

Note 1 to entry: The IUPAC considers specificity as the final stage of selectivity.

[SOURCE: ISO/IEC Guide 99:2007, 4.13, modified — Examples and original notes to entry have been excluded. A new note to entry has been added.]

3.1.15
reference value
quantity value whose associated measurement uncertainty is generally considered small enough so that the value may be used as a basis for comparison with quantity values of the same kind

[SOURCE: ISO/IEC Guide 99:2007, 5.18, modified — Notes to entry have been excluded.]

3.1.16
scope
<of the method>all of the types of *matrix* (3.1.22) to which the method applies, taking into account the range of concentrations involved in validation

3.1.17
scope of validation
all of the types of *matrix* (3.1.22) to which the method and range of concentrations involved in validation applies

3.1.18
scope of validity
all of the types of *matrix* (3.1.22) to which the method and range of concentrations involved in validation applies, and for which future outcomes obtained via the method will be considered valid

3.1.19
quantitative method
method of analysis which determines the quantity or weight fraction of an analyte so that it may be expressed as a numeric value in the appropriate units

3.1.20
reference method
method of analysis recognized by experts or used as a reference by agreement between parties, which gives, or is supposed to give the accepted reference value of the measurand

3.1.21
alternative method
method of analysis used by the laboratory instead of one or several *reference methods* (3.1.20)

3.1.22
matrix
set of properties of the sample and its components other than the analyte

Note 1 to entry: The matrix effect reflects the possible influence that these properties or components can have on the instrumental response. For practical reasons, since the matrix effect can vary in the different stages of analysis (e.g. before or after mineralisation), a type of matrix is defined as a group of materials or products recognized by the analyst as having consistent behaviour with regard to the method of analysis used.

3.1.23
series
set of measurements carried out under a set of repeatability conditions

Note 1 to entry: For example, a series includes measurements carried out on the same day and/or by the same operator.

3.1.24
accuracy profile

combination, in a graphic form, of one or several *β-expectation tolerance intervals* (3.1.25) calculated at different concentrations, and of one or several *acceptance intervals* (3.1.26)

3.1.25
β-expectation tolerance interval
tolerance interval

interval which contains, on average, a defined proportion, β %, of future measurements, obtained according to a given procedure and for a given concentration

Note 1 to entry: The limits of the interval are calculated based on trials conducted for the purpose of validation.

Note 2 to entry: A value of 80 % for β % means that, on average, one out of five results will be outside the limits of the interval at the *limit of quantitation* (3.1.29). See 5.10.

3.1.26
acceptance interval
specification of the performance required for the method, expressed as an acceptable deviation around the reference value

Note 1 to entry: The limits of the interval are set by the client or by statutory requirements, sometimes according to the concentration. They are expressed as ±λ as absolute values and in the units of the measurand, or (1 ± λ) × 100 as relative values.

3.1.27
linearity
<of the method> establishment of a linear relationship between the deduced (or quantified) quantities in the samples and their reference values

Note 1 to entry: Linearity of the method is different from linearity of the response function of the measuring apparatus, which only characterizes the instrumental response during calibration and is not essential for accurate quantitation.

3.1.28
validation sample
control sample
material to which the reference value may be assigned, either because it is a reference material (certified or uncertified), or because the molecule to be assayed has been subjected to standard addition

3.1.29
limit of quantitation
the lowest and/or highest concentration of analyte that may be quantified under the experimental conditions of the method. It corresponds to the lowest and/or highest concentration of the *scope of validity* (3.1.18)

Note 1 to entry: Note 1to entry: According to the SFSTP (French society for pharmaceutical sciences and technology), the limit of quantitation is the smallest quantity of analyte in a sample that may be assayed under the experimental conditions described with a defined level of accuracy.

3.1.30
limit of detection
measured quantity value, obtained by a given measurement procedure, for which the probability of falsely claiming the absence of a component in a material is b, given a probability, α, of falsely claiming its presence

Note 1 to entry: The notation b used in this definition incurs a risk of type II error.

[SOURCE: ISO/IEC Guide 99:2007, 4.18, modified — Original notes to entry have been omitted and a new note to entry has been added.]

3.2 Symbols

A series of i measurements *(*i varying from 1 to I*)*, includes k concentrations *(*k varying from 1 to K*)*, for which j repetitions have been performed *(*j varying from 1 to J*)*. The subscripts are written in the following order: *i,j,k*. The random variables are written in upper case letters and their values in lower case letters. Description of abbreviations used in formulae is given in Table 1.

Table 1 — Meaning of the different abbreviations used in formulae

Symbol	Description
x_{ijk}	Reference value assigned to a calibration standard for series i ($1 \le i \le I$), repetition j ($1 \le j \le J$) and concentration k ($1 \le k \le K$) or Reference value assigned to a validation sample for series i, repetition j and concentration k.
y_{ijk}	Measurement of the instrumental or experimental response observed for a calibration standard or validation sample for series i, repetition j and concentration k.
z_{ijk}	Deduced value for a validation sample for series i, repetition j and concentration k, obtained either by inverse prediction using a calibration model or by direct measurement.
b_{ijk}	Bias expressing the trueness error for a validation sample between the deduced value and its reference value $b_{ijk} = z_{ijk} - x_{ijk}$

4 General principles

4.1 Reminder

The accuracy profile allows a statistical approach to validation. Formula (1) is used to describe a measurement, z, of a measurand, Z, from a laboratory:

$$z = m + B + e \tag{1}$$

where

m is the overall average for the homogeneous sample sent to the laboratories;

B is the bias component of the laboratory under conditions of repeatability;

e is the random error occurring in each measurement, under conditions of repeatability.

As part of an interlaboratory study, the bias component B comes from the laboratory, but it may also come from any other source of uncertainty in an intralaboratory study, such as the day, operator, instrument, etc.

In addition to the statistical methods for calculating the accuracy criteria, the present document also provides details of the organization of data collection and precautions to be taken.

4.2 Various conditions for the estimation of precision

According to its definition, precision can be estimated under various conditions. In any case, precision is quantified based on a standard deviation, be this for repeatability s_r, intermediate precision s_{IP} or reproducibility s_R. A complexity scale may be established between these different standard deviations, according to the number of sources of uncertainty. Figure 3 illustrates this gradation, from conditions of repeatability where there is no identified variation factor and/or systematic variation component for calculating the deviation between repetitions, to the various possibilities for estimating intermediate precision and, finally, conditions of reproducibility for which the number of sources is not known.

To simplify presentation, the notion of series refers to a set of repetitions performed under conditions of repeatability: a series groups together all of the measurements made under the same conditions, e.g. the same day, the same operator or a short period of time. For certain methods applying to samples that are highly unstable over time, the chosen series effect should be the operator rather than the day; the series will thus include repetitions performed by the same operator:

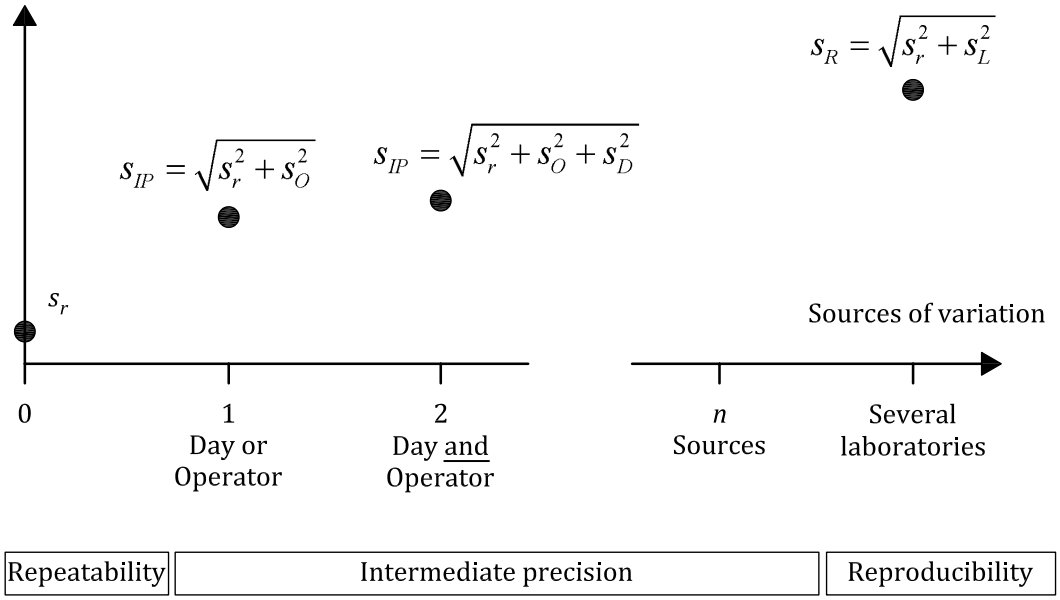


Figure 3 — Various estimations of the precision of a method according to the sources of variation involved

More complicated models may be used, as in the following example, in which different laboratories, days, operators and instruments are combined to give four series in a multi-factorial design with three factors.

Series	Laboratories	Days	Operators	Instruments
1	1	Day 1 (–)	Operator 1 (–)	Instrument 1 (+)
2	1	Day 2 (+)	Operator 1 (–)	Instrument 2 (–)
3	1	Day 1 (–)	Operator 2 (+)	Instrument 2 (–)
4	1	Day 2 (+)	Operator 2 (+)	Instrument 1 (+)

In general, the choice of sources of variation for the measurement series should reflect as best possible the components of variability that are likely to arise upon routine application of the method to be validated.

NOTE For the purposes described in this document, it is essential to collect data in several series and to control the sources of variation. Otherwise, it will not be possible to construct an accuracy profile.

4.3 Accuracy profile

From the intermediate precision or reproducibility standard deviation, calculated according to the calculations described in Annex A, the β-expectation tolerance interval can be obtained, which includes a proportion, β, of future outcomes.

All calculations are performed separately for each concentration k, allowing k precision standard deviations and then k tolerance intervals to be obtained, which are brought together to construct the accuracy profile. Figure 4 shows an example of an accuracy profile constructed using three concentrations, 0,4 mg/L, 2,0 mg/L and 4,0 mg/L, which defines the scope or scope of validation of the method to be validated.

The accuracy profile includes the following graphic elements:

— on the horizontal axis: the theoretical concentrations (the concentration reference values);