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## Reference materials — Guidance for characterization and assessment of homogeneity and stability

*Matériaux de référence — Lignes directrices pour la caractérisation  
et l'évaluation de l'homogénéité et de la stabilité*

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# Contents

Page

Foreword.....	vi
Introduction.....	vii
<b>1 Scope.....</b>	<b>1</b>
<b>2 Normative references.....</b>	<b>1</b>
<b>3 Terms and definitions.....</b>	<b>1</b>
<b>4 Symbols.....</b>	<b>3</b>
<b>5 Conventions.....</b>	<b>4</b>
<b>6 An overview of reference material production.....</b>	<b>5</b>
6.1 General.....	5
6.2 Summary of project design.....	5
6.3 Acquisition of starting material.....	6
6.4 Feasibility studies.....	7
6.5 Reference material processing.....	7
6.6 Homogeneity assessment.....	7
6.7 Stability assessment.....	7
6.8 Choice of measurement procedures.....	7
6.9 Metrological traceability.....	8
6.10 Characterization and uncertainty evaluation.....	8
6.11 Commutability assessment.....	8
6.12 Transport issues.....	8
6.13 Value assignment.....	9
6.14 Stability monitoring.....	9
6.15 Reference materials produced in repeated batches.....	9
<b>7 Assessment of homogeneity.....</b>	<b>9</b>
7.1 Preamble.....	9
7.2 Need for an experimental homogeneity study.....	10
7.3 Properties to be studied.....	11
7.4 Statistically valid sampling schemes.....	11
7.4.1 Minimum number of units for a homogeneity study.....	11
7.4.2 Use of statistical power analysis.....	13
7.4.3 Sampling strategy for a homogeneity study.....	13
7.5 Choice and conduct of the measurement procedure for a homogeneity study.....	14
7.5.1 Choice of measurement procedure.....	14
7.5.2 Conduct of measurements for homogeneity studies.....	14
7.6 Homogeneity study designs.....	16
7.6.1 Objective of a homogeneity study.....	16
7.6.2 The basic homogeneity study design – measurement in a single run.....	17
7.6.3 Randomized block design.....	18
7.6.4 Balanced nested design.....	18
7.6.5 Alternative strategies.....	19
7.7 Evaluating a homogeneity study.....	19
7.7.1 Initial inspection for measurement trends and outliers.....	19
7.7.2 Inspection for processing trends.....	20
7.7.3 Evaluation of the between-unit term – basic design.....	20
7.7.4 Evaluation of the between-unit term – randomized block design.....	21
7.7.5 Evaluation of the between-unit term – balanced nested design.....	21
7.7.6 Other homogeneity designs and alternative estimation methods.....	22
7.8 Insufficient repeatability of the measurement procedure.....	22
7.9 Within-unit homogeneity.....	23
7.9.1 Assessing the need for within-unit homogeneity study.....	23
7.9.2 Testing for significant within-unit heterogeneity.....	23
7.9.3 Assessing minimum sample size.....	25

7.10	Check for sufficient homogeneity .....	26
7.11	Uncertainty evaluation from homogeneity studies .....	26
<b>8</b>	<b>Assessment and monitoring of stability .....</b>	<b>26</b>
8.1	Preamble .....	26
8.2	Assessment of stability .....	28
8.2.1	Requirement for stability assessment .....	28
8.2.2	Types of (in)stability .....	28
8.2.3	General methods for assessment of stability .....	28
8.2.4	Need for experimental study of stability .....	29
8.3	Classification of stability studies .....	29
8.3.1	General .....	29
8.3.2	Classification according to conditions of measurement .....	30
8.3.3	Classification according to stability study duration and conditions .....	30
8.3.4	Classification by study objective .....	31
8.3.5	Designs for different storage and treatment conditions .....	32
8.4	General requirements for effective stability studies .....	32
8.4.1	Overview of requirements .....	32
8.4.2	Selection of units .....	32
8.4.3	Suitable measurement procedure(s) for stability studies .....	33
8.4.4	Appropriate experimental design .....	33
8.5	Evaluation of stability study results .....	34
8.5.1	General considerations for stability study data treatment .....	34
8.5.2	The basic stability study: multiple points in time at a single storage condition .....	35
8.5.3	Isochronous designs .....	36
8.5.4	Accelerated stability studies with multiple exposure conditions .....	38
8.5.5	Additional sources of random variation in stability studies .....	41
8.6	Action on finding of a significant trend in a stability study .....	42
8.7	Uncertainty evaluation from stability studies .....	42
8.7.1	General considerations for uncertainty evaluation from stability studies .....	42
8.7.2	Sources of uncertainty in predicted change over time .....	43
8.7.3	Estimation of stability uncertainties in the absence of significant trends .....	43
8.7.4	Evaluation of stability uncertainties in the case of a known significant trend .....	44
8.8	Estimation of storage lifetime ("shelf life") from a stability study .....	44
8.9	Instructions for use related to management of stability .....	44
8.10	Stability monitoring .....	45
8.10.1	Requirements for monitoring .....	45
8.10.2	Choice of initial monitoring point and monitoring interval(s) .....	45
8.10.3	Experimental approaches and evaluation for stability monitoring .....	47
<b>9</b>	<b>Characterization of the material .....</b>	<b>48</b>
9.1	Preamble .....	48
9.2	Establishing metrological traceability .....	49
9.2.1	Principle .....	49
9.2.2	Metrological references .....	49
9.2.3	Types of measurands .....	50
9.2.4	Effect of sample preparation or pre-treatment .....	50
9.2.5	Verification of traceability .....	51
9.3	Characterization using a single reference measurement procedure (as defined in ISO/IEC Guide 99) in a single laboratory .....	51
9.3.1	Characterization by a reference measurement procedure without direct comparison with a CRM of the same kind .....	51
9.3.2	Characterization by value transfer from a reference material to a closely matched candidate reference material using a single measurement procedure performed by one laboratory .....	52
9.3.3	Selection of RM units for single-laboratory characterization .....	53
9.3.4	Formulation methods .....	54
9.4	Characterization of a non-operationally defined measurand using two or more methods of demonstrable accuracy in one or more competent laboratories .....	54

9.4.1	Concept .....	54
9.4.2	Study design .....	55
9.4.3	Evaluation .....	56
9.4.4	Single-laboratory multi-method studies .....	57
9.5	Characterization of an operationally defined measurand using a network of competent laboratories .....	58
9.5.1	Concept .....	58
9.5.2	Study setup .....	58
9.5.3	Evaluation .....	58
9.6	Purity .....	58
9.6.1	General .....	58
9.6.2	Direct determination of purity .....	59
9.6.3	Indirect determination of purity .....	59
9.7	Identity .....	60
9.7.1	Materials certified based on provenance .....	60
9.7.2	Materials certified for identity based on measurements .....	60
9.8	Presence/absence .....	62
9.9	Ordinal scales .....	63
9.10	Qualitative properties .....	63
9.11	Characterization of non-certified values .....	63
<b>10</b>	<b>Evaluating measurement uncertainty .....</b>	<b>63</b>
10.1	Basis for evaluating the uncertainty of a property value of a CRM .....	63
10.2	Basic model for a batch characterization .....	64
10.3	Uncertainty sources .....	64
10.4	Coverage intervals and factors .....	65
<b>Annex A</b>	<b>(informative) Design and evaluation of studies for the characterization of a method-independent measurand using two or more methods of demonstrable accuracy in one or more competent laboratories .....</b>	<b>66</b>
<b>Annex B</b>	<b>(informative) Statistical approaches .....</b>	<b>77</b>
<b>Annex C</b>	<b>(informative) Examples .....</b>	<b>89</b>
<b>Annex D</b>	<b>(informative) Measurement uncertainty evaluation .....</b>	<b>99</b>
<b>Bibliography</b>	<b>.....</b>	<b>101</b>

## Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see [www.iso.org/directives](http://www.iso.org/directives)).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see [www.iso.org/patents](http://www.iso.org/patents)).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: [www.iso.org/iso/foreword.html](http://www.iso.org/iso/foreword.html)

This document was prepared by Technical Committee ISO/REMCO, the Reference Materials Committee of ISO.

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## Introduction

The production of reference materials (RMs) is a key activity for the improvement and maintenance of a worldwide coherent measurement system. As detailed in ISO Guide 33[1], RMs with different characteristics are used in measurements, such as calibration, quality control, proficiency testing and method validation, as well as for the assignment of values to other materials. Certified reference materials (CRMs) are also used to confirm or establish metrological traceability to conventional scales, such as the octane number, hardness scales and pH.

To be comparable across borders and over time, measurements need to be traceable to appropriate and stated references. CRMs play a key role in implementing the concept of traceability of measurement results in chemistry, biology and physics among other sciences dealing with substances and materials. Laboratories use these CRMs as readily accessible measurement standards to establish traceability of their measurement results to International Standards. The property values carried by a CRM can be made traceable to the International System of Units (SI) or other internationally agreed references during production. This document explains how approaches can be developed that will lead to well established property values, which are made traceable to appropriate stated references.

For reference material producers (RMPs), there is an International Standard and three ISO Guides that support the production and certification of RMs to ensure that the quality of the RMs meets the requirements of the end users.

- ISO 17034 outlines the general requirements to be met by an RMP to demonstrate competence.
- ISO Guide 35 provides more specific guidance on technical issues and explains the concepts for processes such as the assessment of homogeneity, stability and characterization for the certification of RMs.
- ISO Guide 31[2] describes the contents of certificates for CRMs, and of accompanying documents for other RMs, respectively.
- ISO Guide 30[68] contains the terms and definitions related to reference materials.

Alongside developments in RM production approaches, the range of classes of RMs is growing with advances in technology, increasing the need for more widely applicable technical guidance in RM production. In addition, increasing use of ISO/IEC 17025[52] and ISO 15189[71] by laboratories has led to greater demand for clear statements of metrological traceability.

This document provides detailed guidance on a larger range of homogeneity study designs, and describes a wider range of stability management strategies than ISO Guide 35:2006. It also contains specific provisions concerning the establishment of metrological traceability in RM production.





# Reference materials — Guidance for characterization and assessment of homogeneity and stability

## 1 Scope

This document explains concepts and provides approaches to the following aspects of the production of reference materials:

- the assessment of homogeneity;
- the assessment of stability and the management of the risks associated with possible stability issues related to the properties of interest;
- the characterization and value assignment of properties of a reference material;
- the evaluation of uncertainty for certified values;
- the establishment of the metrological traceability of certified property values.

The guidance given supports the implementation of ISO 17034. Other approaches may also be used as long as the requirements of ISO 17034 are fulfilled.

Brief guidance on the need for commutability assessment (6.11) is given in this document, but no technical details are provided. A brief introduction for the characterization of qualitative properties (9.6 to 9.10) is provided together with brief guidance on sampling such materials for homogeneity tests (Clause 7). However, statistical methods for the assessment of the homogeneity and stability of reference materials for qualitative properties are not covered. This document is also not applicable to multivariate quantities, such as spectral data.

## 2 Normative references

The following documents are referred to in the text in such a way that some or all of their 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 3534-2, *Statistics — Vocabulary and symbols — Part 2: Applied statistics*

ISO 3534-3, *Statistics — Vocabulary and symbols — Part 3: Design of experiments*

ISO Guide 30, *Reference materials — Selected terms and definitions*

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

NOTE The *International vocabulary of metrology* will hereafter be referred to as the “VIM”.

## 3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO Guide 30, ISO/IEC Guide 99, ISO 3534-2, ISO 3534-3 and the following apply. The definitions in ISO Guide 30 take precedence where more than one definition for the same term exists.

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

- ISO Online browsing platform: available at <http://www.iso.org/obp>

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

## 3.1 reference material

### RM

material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process

Note 1 to entry: RM is a generic term.

Note 2 to entry: Properties can be quantitative or qualitative, e.g. identity of substances or species.

Note 3 to entry: Uses may include the calibration of a measurement system, assessment of a measurement procedure, assigning values to other materials, and quality control.

Note 4 to entry: ISO/IEC Guide 99:2007<sup>[3]</sup> has an analogous definition (5.13), but restricts the term “measurement” to apply to quantitative values. However, ISO/IEC Guide 99:2007, 5.13, Note 3 (VIM), specifically includes qualitative properties, called “nominal properties”.

[SOURCE: ISO Guide 30:2015, 2.1.1]

## 3.2 certified reference material

### CRM

reference material (RM) characterised by a metrologically valid procedure for one or more specified properties, accompanied by an RM certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability

Note 1 to entry: The concept of value includes a nominal property or a qualitative attribute such as identity or sequence. Uncertainties for such attributes may be expressed as probabilities or levels of confidence.

Note 2 to entry: Metrologically valid procedures for the production and certification of RMs are given in, among others, ISO 17034 and ISO Guide 35.

Note 3 to entry: ISO Guide 31<sup>[2]</sup> gives guidance on the contents of RM certificates.

Note 4 to entry: ISO/IEC Guide 99:2007<sup>[3]</sup> has an analogous definition (5.14).

[SOURCE: ISO Guide 30:2015, 2.1.2]

## 3.3 measurement model

mathematical relation among all quantities known to be involved in a measurement  
[SOURCE: ISO/IEC Guide 99:2007, 2.48<sup>[3]</sup>]

## 3.4 property value

<of a reference material (RM)> value corresponding to a quantity representing a physical, chemical or biological property of an RM

[SOURCE: ISO Guide 30:2015, 2.2.1]

## 3.5 certified value

value, assigned to a property of a reference material (RM), that is accompanied by an uncertainty statement and a statement of metrological traceability, identified as such in the RM certificate

[SOURCE: ISO Guide 30:2015, 2.2.3]

**3.6****indicative value**

information value

informative value

value of a quantity or property of a reference material, which is provided for information only

Note 1 to entry: An indicative value cannot be used as a reference in a metrological traceability chain.

[SOURCE: ISO Guide 30:2015, 2.2.4]

**3.7****calibrant**

reference material used for calibration of equipment or a measurement procedure

[SOURCE: ISO Guide 30:2015, 2.1.21]

**3.8****quality control material**

reference material used for quality control of a measurement

[SOURCE: ISO Guide 30:2015, 2.1.22]

**3.9****isochronous stability study**

experimental study of reference material stability in which units exposed to different storage conditions and times are measured in a short period of time

**3.10****production**

&lt;of a reference material (RM)&gt; all necessary activities and tasks leading to the release and maintenance of an RM (certified or non-certified)

Note 1 to entry: Activities include, for example, planning, control, material handling and storage, material processing, assessment of homogeneity and stability, characterization, assignment of property values and their uncertainties, authorization and issue of RM certificates or other statements.

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[SOURCE: ISO Guide 30:2015, 2.3.7]

**4 Symbols**

$a$	number of reference material units in a homogeneity study
$d$	measurement bias
$k$	coverage factor or (as subscript) index
$L_d$	a limit of detection (minimum detectable value of the net state variable) calculated using the methods of ISO 11843-1 <sup>[48]</sup>
$N_{\min}$	minimum number of RM units for a homogeneity study for batch sizes over 100 units
$N_{\text{prod}}$	number of RM units produced in a single batch
$n_r$	number of runs in a blocked or nested homogeneity study design
$p$	number of laboratory means in an interlaboratory certification exercise
$s_{\text{bb}}$	between-unit component of variance from a homogeneity study, expressed as a standard deviation

$s_r$	repeatability standard deviation
$s_R$	reproducibility standard deviation
$t_{lts}$	duration of a long term stability study
$U_{CRM}$	expanded uncertainty associated with a property value of the CRM
$u_{bb}$	standard uncertainty associated with between-unit variability
$u_{char}$	standard uncertainty associated with a value assigned in a characterization study
$u_{CRM}$	standard uncertainty associated with property value of the CRM
$u_{trg}$	target measurement uncertainty, expressed as standard uncertainty, for the value of a property to be certified
$u_{hom}$	standard uncertainty associated with heterogeneity
$u_{lts}$	standard uncertainty associated with long term stability
$u_{mon}$	standard uncertainty associated with a value obtained by measuring an RM at a monitoring point
$u_{trn}$	standard uncertainty associated with the transport stability of the material
$u_{wb}$	standard uncertainty associated with within-unit heterogeneity
$x_{CRM}$	property value of a CRM
$\hat{x}$	estimated value obtained from a robust statistical estimator
$x_{mon}$	value obtained by measuring an RM property value at a monitoring point
$x$	amount-of-substance fraction
$y_{char}$	value assigned to a reference material in a characterization study

Additional symbols used in particular subclauses are defined on first use in the text.

## 5 Conventions

In this document, the following conventions are used.

- A measurand is specified in such a way that there exists a unique 'true value'.
- All probability assessments described in this document assume normality unless otherwise stated.
- Throughout this document, the law of propagation of uncertainty is used for the combination of measurement uncertainty contributions. Other methods of evaluating measurement uncertainty may also be applied, and in some cases it is necessary to do so. Further guidance on these matters is given in ISO/IEC Guide 98-3, "*Uncertainty of measurement — Part 3: Guide to the expression of uncertainty in measurement (GUM:1995)*" and its supplements (see References [5] and [6]).

NOTE 1 Variation between units associated with heterogeneity and changes due to instability might not be normally distributed and can result in asymmetric distributions.

NOTE 2 The "*Guide to the expression of uncertainty in measurement*" will hereafter be referred to as the "GUM".

## 6 An overview of reference material production

### 6.1 General

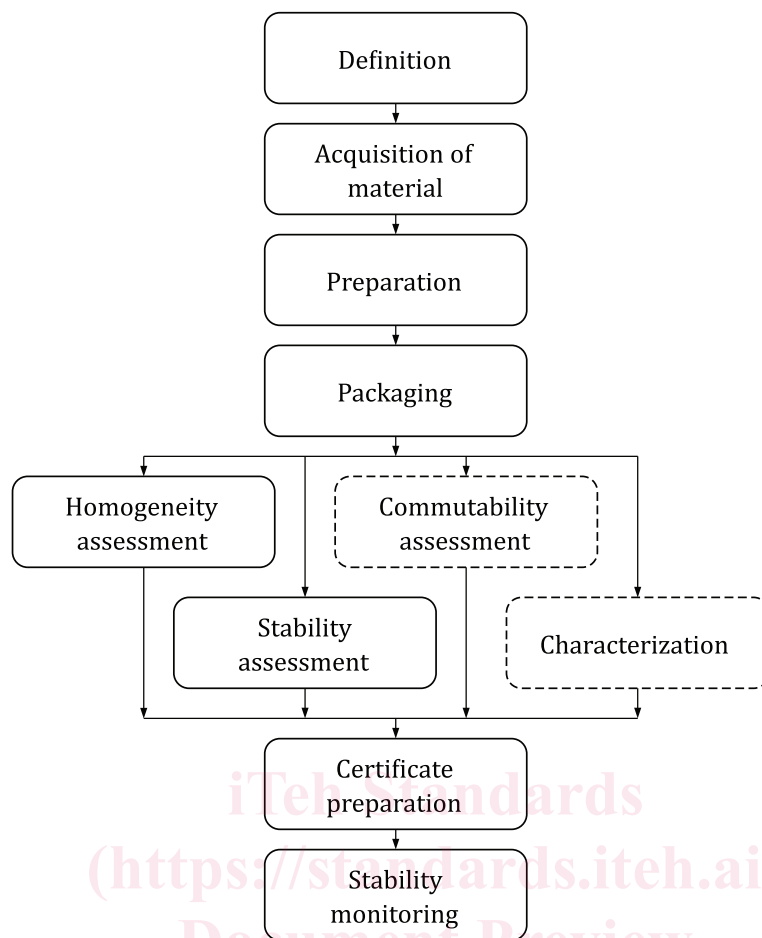
The production and distribution of an RM require careful planning prior to undertaking any actual activity in the project. The following subclauses provide a brief overview of the steps involved in the production of a reference material followed by a description of the main issues involved in planning each step. Detailed guidance on homogeneity assessment, stability assessment and characterization is given in [Clauses 7, 8 and 9](#), respectively.

### 6.2 Summary of project design

The production of a reference material involves the following steps:

- a) definition of the RM, i.e. the matrix, the properties to be characterized and their desired levels, the intended use of the material, and for CRMs, the target uncertainty<sup>[72]</sup>;
- b) design of a procedure for the sourcing of the material;
- c) design of a reference material manufacturing and/or preparation procedure;
- d) selection of measurement procedures appropriate for characterization, homogeneity and stability studies;
- e) consideration of metrological traceability for each measured property, particularly for CRMs, for which a statement of metrological traceability is required;
- f) assessment of homogeneity;
- g) assessment of stability;
- h) assessment of commutability (if required);
- i) characterization of the reference material;
- j) combination of the results from homogeneity studies, stability studies, and, for CRMs, evaluation of the measurement uncertainties of certified values;
- k) preparation of a certificate or product information sheet and, if appropriate, a report on the production and/or certification;
- l) specification of storage and transportation conditions;
- m) post-production monitoring of stability.

The main stages are shown schematically in [Figure 1](#).



NOTE 1 The figure provides a schematic outline of the main steps in producing and maintaining a reference material. Boxes with dashed outlines are not always necessary.

NOTE 2 'Packaging' in this diagram includes subdivision into individual units in suitable containers for distribution.

NOTE 3 In this diagram, 'Certificate preparation' includes all types of documentation that could be provided with a reference material, including a certificate, product information sheet, certification report, etc.

**Figure 1 — Schematic outline of a reference material project**

### 6.3 Acquisition of starting material

The first task in an RM production project is the acquisition of a sufficient amount of starting material(s) with the desired properties. The production of materials with particular properties is considered briefly in 9.3.4. The amount of material needed is determined by the following:

- the number of units of the RM needed for distribution over the expected life of the RM;
- the number of units needed for the homogeneity study;
- the number of units needed for the stability study;
- the number of units needed for the characterization of the candidate RM;
- the number of units required for monitoring stability over the expected lifetime of the material;
- the planned size of each RM unit, which has to be sufficient for at least one measurement;
- the need for one or more feasibility studies;