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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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Foreword

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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).

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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

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

This fourth edition cancels and replaces the third edition (ISO Guide 35:2006).

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[3] 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[2] gives guidance on the contents of RM certificates.

Note 4 to entry: ISO/IEC Guide 99:2007[3] 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[3]]

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
<of a reference material (RM)> 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.

[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[48]
N_{min}	minimum number of RM units for a homogeneity study for batch sizes over 100 units
N_{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_{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) A measurand is specified in such a way that there exists a unique 'true value'.

b) All probability assessments described in this document assume normality unless otherwise stated.

c) 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[72];

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;

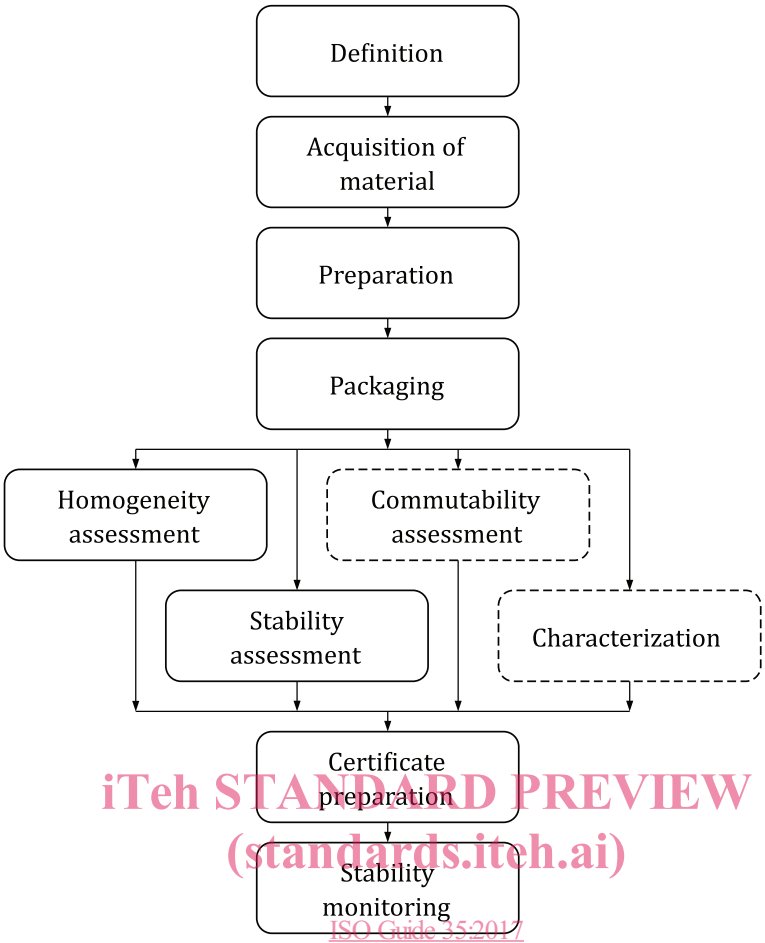
j) combination of the results from homogeneity studies, stability studies, and, for CRMs, evaluation of the measurement uncertainties of certified values;

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;

— optionally, additional units to cover contingencies such as, for example, follow-up studies to respond to customer queries, future recertification required by a significant change in the storage conditions, or extension of the number of certified properties.

The number of units of a candidate RM that are needed for distribution is often, at least in part, a commercial issue and should be carefully considered before commissioning the collection and processing of the material. In addition, the expected long-term stability of the material in storage can influence the amount of material that can usefully be produced. It may be prudent to limit the number of units produced for less stable materials to avoid wastage due to unavoidable degradation over time.

6.4 Feasibility studies

Feasibility studies are short studies intended to address concerns about the feasibility of producing and characterizing a sufficiently homogeneous and stable RM. For example, questions such as the best way of preparing the RM or ensuring sufficient stability of the material can be answered by small-scale feasibility studies early in the project[7].

Where characterization is expected to be performed through the use of an interlaboratory study, a feasibility study can identify possible sources of error and enable participants involved in the characterization to optimize their equipment and procedures.

NOTE In a feasibility study intended to test or improve the capabilities of participants in an interlaboratory characterization exercise (see Clause 9), use of a material different from the candidate RM can avoid undue bias in participant results arising from prior knowledge of the candidate RM.

6.5 Reference material processing

Processing can involve a range of processes, including, for example:

— synthesis, manufacture or formulation of a synthetic reference material;

— drying, lyophilisation, milling, and/or filtration for natural materials;

— addition of stabilizing agents;

— homogenization prior to packaging.

The particular procedures used depend on the particular material and usually require expert guidance.

6.6 Homogeneity assessment

Homogeneity is an important requirement for all RMs and includes both within- and between-unit homogeneity. Between-unit homogeneity is important to ensure that each RM unit carries the same value for each property; within-unit homogeneity is important where subsamples can be taken for measurement by users of the material. Clause 7 gives detailed guidance on homogeneity assessment.

6.7 Stability assessment

RMs should be sufficiently stable for their intended use, so that the end user can rely on the assigned value at any point within the period of validity of the certificate. Typically, it is important to consider stability under long-term storage conditions, under transport conditions and, where applicable, the storage conditions at the RM user's laboratory. This can include consideration of stability after opening, if re-use is permitted. Clause 8 provides detailed guidance on stability assessment.

6.8 Choice of measurement procedures

In a reference material production project, each step that requires measurements may use different measurement procedures because, for example, characterization generally requires minimally biased measurement procedures with low uncertainty; homogeneity studies primarily require the best