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Reference materials — Approaches for characterization and assessment of homogeneity and stability

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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 document 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 of 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 www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 334, *Reference materials*.

This first edition cancels and replaces ISO Guide 35:2017, which has been technically revised.

The main changes are as follows:

— technical requirements for the characterization and the assessment of homogeneity and stability of reference materials as stipulated in ISO 17034 is reiterated in this document with additional guidance on approaches that can be used.

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 production of reference materials (RMs) is a key activity for the improvement and maintenance of a worldwide coherent measurement system. As detailed in ISO 33403[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), this document refers to ISO 17034, ISO 33401[2)] and ISO Guide 30 that support the production and certification of RMs:

— ISO 17034 outlines the general requirements to be met by an RMP to demonstrate competence;

— ISO 33401 describes the contents of certificates for CRMs and of accompanying documents for other RMs;

— ISO Guide 30 contains 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 and ISO 15189 by laboratories has led to greater demand for clear statements of metrological traceability.

This document describes examples of possible designs for homogeneity, stability and characterization studies that are in line with ISO 17034. It also contains specific provisions concerning the establishment of metrological traceability in RM production.

1) Under preparation. Stage at the time of publication: ISO/FDIS 33403:2023.

2) Under preparation. Stage at the time of publication: ISO/DIS 33401:2023.

Reference materials — Approaches 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 (RMs):

— 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 (RM);

— the evaluation of uncertainty for certified values;

— the establishment of the metrological traceability of certified values.

The guidance given supports the implementation of ISO 17034. Other approaches can 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 9.8) is provided, together with brief guidance on sampling such materials for homogeneity tests (7.4.1.2). However, statistical methods for the assessment of the homogeneity and stability of RMs for qualitative properties are not covered. This document is also not applicable to multivariate quantities, such as spectral data.

NOTE ISO 33406[3)] gives more information on the production of RMs with one or more qualitative property values.

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)*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 3534-2, ISO 3534-3, ISO Guide 30, ISO/IEC Guide 99 and the following apply.

3) Under preparation. Stage at the time of publication: ISO/DIS 33406:2023.

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

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

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

3.1
classical stability study
experimental study of reference material stability in which individual samples are prepared at the same time and are measured as time elapses.

3.2
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, see Figure 6.

4 Symbols

a	number of RM 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
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_{bu}	between-unit component of variance from a homogeneity study, expressed as a standard deviation
s_r	repeatability standard deviation
s_R	within laboratory reproducibility standard deviation
t_{lts}	duration of a long-term stability study
U_{CRM}	expanded uncertainty associated with a property value of the certified reference material (CRM)
u_{bu}	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 the 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_{wu} 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 measurement result for a property value

y_{char} value assigned to a RM in a characterization study

$M_{between}$ between-group mean square term from analysis of variance (ANOVA)

M_{within} within-group mean square term from analysis of variance (ANOVA)

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 can 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 and its supplements.

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

NOTE 2 ISO/IEC Guide 98-3 will hereafter be referred to as the “GUM”.

6 Overview of reference material (RM) production

6.1 General

The production and distribution of an RM require careful planning prior to undertaking any actual activity in the project. Subclauses 6.2 to 6.15 provide a brief overview of the steps involved in the production of an RM followed by a description of the main issues involved in planning each step. Detailed guidance on homogeneity assessment, stability assessment and characterization are given in Clauses 7, 8 and 9, respectively.

6.2 Summary of project design

The production of an RM involves the following steps:

a) specification 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[21];

b) design of a procedure for the sourcing of the material;

c) design of an RM manufacturing and/or preparation procedure;

d) packaging and labelling

e) selection of measurement procedures appropriate for characterization, homogeneity and stability studies;

f) consideration of metrological traceability for each measured property, particularly for CRMs, for which a statement of metrological traceability is required;

g) assessment of homogeneity;

h) assessment of stability;

i) assessment of commutability (if required);

j) characterization of the RM;

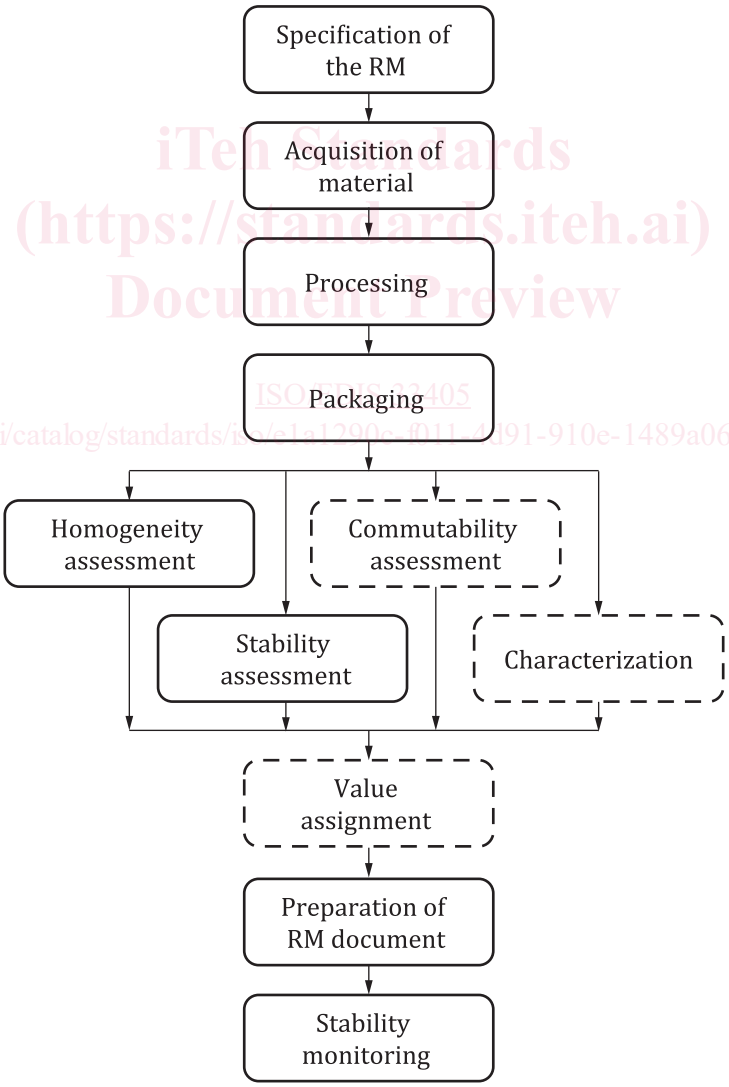
k) combination of the results from homogeneity studies, stability studies and, for CRMs, evaluation of the measurement uncertainties of certified values;

l) preparation of a certificate or product information sheet and, if appropriate, a report on the production and/or certification as per the guidance provided in ISO 33401;

m) specification of storage and transportation conditions and the planned lifespan;

n) post-production monitoring of stability.

The main stages of the project design as listed in 6.2 are shown schematically in Figure 1. Some aspects of the project design are described in more detail in 6.3 to 6.15.



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

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

Figure 1 — Schematic outline of a reference material project

6.3 Acquisition of starting material

The first task in an RM production project, after the specification of the RM, is the acquisition of a sufficient amount of starting material(s) with the desired properties. 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 an 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 is advisable 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[22].

Where characterization is expected to be performed with 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 RM;

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

— addition of stabilizing agents;

— homogenization prior to packaging.

The 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

In accordance with ISO 17034, RMs shall 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 repeated use of the RM is permitted. Clause 8 provides detailed guidance on stability assessment.

6.8 Choice of measurement procedures

In an RM production project, each step that requires measurements can use different measurement procedures because, for example, characterization generally requires minimally biased measurement procedures with low uncertainty; homogeneity studies primarily require the best available repeatability; and classical stability studies typically require measurement procedures that show good precision over time within the same laboratory. The choice of measurement procedures for homogeneity studies, stability studies and characterization are considered in Clauses 7, 8 and 9, respectively.

6.9 Metrological traceability

Metrological traceability is key to ensuring the comparability of measurement results over time and between locations, including those used to characterize RMs. By definition, CRMs are accompanied by a statement of metrological traceability for each certified value. The proper choice of the stated references to which metrological traceability of the property values is established, is essential for CRMs, because CRMs are primarily used to make measurement results traceable. Establishment of metrological traceability is considered in detail in 9.2.

6.10 Characterization and uncertainty evaluation

Characterization refers to the determination of the property values of the relevant properties of an RM, as part of the production process. Characterization of an RM is described in Clause 9. For CRMs, certified values are accompanied by an associated uncertainty; the evaluation of the uncertainty of the certified value is considered in Clause 10.

6.11 Commutability assessment

The commutability of an RM relates to the ability of the RM, characterized by one measurement procedure (usually a reference procedure) to act as a calibrator or quality control (QC) material for a second measurement or testing procedure applied to routine test materials. This is particularly important where different measurement procedures can respond very differently to different types of test materials. Commutability assessment is not required for all RMs but is required for certain classes of RM.

Current ISO/TC 334 information on commutability assessment[23] states that:

"An RM producer should conduct an assessment of commutability where:

a) the intended use requires commutability of calibration or quality control materials, and

b) the RM producer warrants that the material is fit for the intended use.