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
ISO GUIDE 35:2017(E)

Contents

Foreword vi
Introduction vii

1 Scope 1
2 Normative references 1
3 Terms and definitions 1
4 Symbols 3
5 Conventions 4
6 An overview of reference material production 5
   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

7 Assessment of homogeneity 9
   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
ISO GUIDE 35:2017(E)

7.10 Check for sufficient homogeneity ........................................................................... 26
7.11 Uncertainty evaluation from homogeneity studies .................................................. 26

8 Assessment and monitoring of stability .................................................................... 26
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 intervals .............................. 45
  8.10.3 Experimental approaches and evaluation for stability monitoring .................... 47

9 Characterization of the material ................................................................................. 48
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

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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
10 Evaluating measurement uncertainty .................................... 63
  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
Annex A (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 ........................................ 66
Annex B (informative) Statistical approaches ........................................ 77
Annex C (informative) Examples ............................................. 89
Annex D (informative) Measurement uncertainty evaluation .................. 99
Bibliography ..................................................................... 101
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).

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).

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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.

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 3534-3, 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
ISO GUIDE 35:2017(E)


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”.


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.


3.3 measurement model
mathematical relation among all quantities known to be involved in a measurement


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.


3.7 calibrant
reference material used for calibration of equipment or a measurement procedure


3.8 quality control material
reference material used for quality control of a measurement


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.


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
\( N_{\text{min}} \) 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
\( s_{bb} \) between-unit component of variance from a homogeneity study, expressed as a standard deviation
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### ISO GUIDE 35:2017(E)

**\( s_r \)** repeatability standard deviation

**\( s_R \)** reproducibility standard deviation

**\( t_{lt} \)** 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

**\( u_{ts} \)** standard uncertainty associated with long term stability

**\( u_{mon} \)** standard uncertainty associated with a value obtained by measuring an RM at a monitoring point

**\( u_{trm} \)** 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".

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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;

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.
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
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 is 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 reference materials. By definition, CRMs are accompanied by a statement of metrological traceability for each certified property 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 a statement of measurement uncertainty; the evaluation of uncertainty 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 some important classes of RM.

NOTE Current ISO/REMCO information on commutability assessment states that:

"A reference material producer should conduct an assessment of commutability where
a) the intended use requires commutability of calibration or quality control materials,
and

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

NOTE 1 Demonstration of commutability is usually required when the intended use includes calibration or quality control in biological measurement, and is not usually required when the intended use does not include biological measurement and the procedure is known to be adequately specific for the measurand in the matrix of the reference material and the intended routine samples.

NOTE 2 It is not usually necessary to establish commutability when the reference material and its origin are obtained from sources and handled the same as samples that would be tested for customers, for example, matrix reference materials.

6.12 Transport issues

Nearly all RMs have to be transported to the location of use. The means and conditions of transport of an RM after production are relevant to the need for stability studies (see Clause 8) and it is therefore useful to consider transport conditions at an early stage in the project.

NOTE 1 National and/or international transport regulations may limit the options for transport, prohibit the transport of some materials, or require specific packaging or precautions for safety or other reasons.

NOTE 2 The time taken for official procedures such as customs or other border control clearance can increase shipment times for some destinations.
6.13 Value assignment

Value assignment is the process of combining the results from the homogeneity and stability assessment with the results from the characterization studies to determine the assigned values and their uncertainties. These values are subsequently issued on a certificate or product information sheet.

6.14 Stability monitoring

Most reference materials are stored for extended periods at the RM producer's premises or by distributors. Since stability assessment cannot usually anticipate all changes that may occur, it is usually necessary, as a part of managing the risks associated with possible instability, to monitor the property values of materials held for extended periods. Because the requirements for monitoring depend in part on knowledge obtained during stability assessment, 8.10 includes guidance on stability monitoring.

6.15 Reference materials produced in repeated batches

The need for experimental study of some characteristics (particularly homogeneity, stability and commutability) can be reduced where the material is produced in a repeat production run following an established procedure. Reliance on prior experience is reasonable so long as:

a) the process for producing batches of the RM has not changed in any way that might adversely affect the end use;

b) the materials used in production of the RM have not changed in any way that might adversely affect the end use;

c) materials previously produced by the same process have shown no failures attributable to the production process, either during routine monitoring or by users; and

d) the requirements for the material are reviewed regularly, taking account of the intended use of the material at the time of the review, to ensure that the production process remains fit for purpose.

Consistent performance of the production process should be checked, for example by comparing the property values of samples from successive batches under repeatability conditions.

7 Assessment of homogeneity

7.1 Preamble

Most RMs are prepared as batches of ‘units’ (e.g. bottles, vials or test pieces). It is important that all distributed units are the same within the stated uncertainty for each property value and, unless sold as single-use units, that the material within each unit is uniform. ISO 17034 accordingly requires the assessment of the homogeneity of a reference material (RM).

Homogeneity can refer either to variation of a property value between separate units of the material, or to variation within each unit. It is always necessary to assess the between-unit variation. Where the intended use permits the use of part of a unit – for example, a small portion of a solid or liquid material, or a small region of the surface – it is also usually necessary either to assess the within-unit variability of the material (within-unit heterogeneity) or to provide instructions for use that control the impact of within-unit heterogeneity. These instructions can include, for example, remixing of the sample and, for granular materials, a minimum sample size, because the within-unit heterogeneity is directly reflected in the minimum size of subsample that is representative for the whole unit.

The assessment of homogeneity may include the use of prior evidence (including prior experimental evidence) of the homogeneity of the material, performing an experimental homogeneity study on the candidate reference material, or both. In most cases, an experimental study is necessary. Exceptions include, for example, batches of a highly homogeneous material, such as a solution for which previous experimental studies have demonstrated that packaging and storage do not affect the homogeneity; or
the production of materials for which each reference material unit has a separate assigned value. 7.2 gives further details about the circumstances and types of material requiring experimental study.

The results of an experimental homogeneity study are usually also used for the calculation of one of the uncertainty components in the certification model (see Clause 10). The magnitude of this uncertainty component can vary widely compared with other components of the uncertainty, depending on the nature of the RM and of the certified property.

To undertake a homogeneity study, a subset of units, typically 10 to 30, is chosen from the batch using a suitable sampling scheme, property values are measured for each unit using a suitable measurement procedure and the results are assessed using appropriate statistical methods to obtain information on, for example, between-unit variability and within-unit variability of the material.

To obtain reliable results, it is important to
— choose the properties to be studied,
— select a representative subset of units,
— choose a suitable measurement procedure with sufficient repeatability and selectivity,
— make the measurements under suitable conditions following an appropriate experimental design, and
— conduct the statistical analysis using valid statistical methods.

7.3 to 7.7 provide guidance on each of these steps. Examples of calculations are provided in Annex C.

Historically, homogeneity studies have tested for statistically significant between-unit differences compared with measurement precision in order to decide whether a material is homogeneous or not. This approach is not taken in this document; rather, emphasis is placed on deciding whether the between-unit standard deviation is sufficiently small for the intended end use. Statistical tests of significance may, however, be of use in RM production, for example in order to decide whether further processing is required to reduce heterogeneity to insignificance compared with routine measurement precision. If statistical tests are used, however, the homogeneity experiment should be capable of detecting important heterogeneity, in turn requiring a sufficient combination of precision of the measurement procedure, number of RM units and number of replicates per unit. Statistical power calculations (7.4.2) can assist in ensuring a sufficiently effective test.

7.2 Need for an experimental homogeneity study

Materials of natural origin or with complex matrices, such as foodstuffs, soils, ores and alloys, are typically heterogeneous in composition. Although the magnitude of between-unit differences can sometimes be small or even negligible after homogenization, in other cases, between-unit differences can remain larger than the uncertainty arising from characterization. RMs prepared from such heterogeneous materials should therefore be subjected to an experimental homogeneity study.

RMs prepared as pure compounds or solutions of pure compounds (if certified for purity; not for impurities) are expected to have a high degree of homogeneity. These materials can, however, also show some heterogeneity, for example, due to a density gradient, localized contamination, evaporation of solvent during processing or filling, variations in residual solvent content, or metals containing variable amounts of occluded gases. Furthermore, certified values for such materials are often expected to have very small uncertainties, making even a small amount of heterogeneity potentially important. Even in cases where the material is expected to be sufficiently homogeneous for most intended uses, homogeneity should be verified. Verification may include a complete homogeneity study or other check (for example, a check on melting point consistency between units of a pure organic material).

An experimental study of the homogeneity of a material is not essential in the following cases:
— when the material is a repeat production run of a previous material that was produced following the same procedure and that has been shown by experiment to be sufficiently homogeneous; or

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— where the production process has been validated and thereby shown to consistently produce sufficiently homogeneous batches of material.

Examples of materials that are sometimes produced in this way include ethanol calibration solutions or elemental calibration solutions prepared by mass and thoroughly mixed to ensure that the mixture will be sufficiently homogeneous for the intended use.

Where assurance of homogeneity relies on a validated production process, quality control procedures should be used to confirm consistent operation of the production process. Such procedures may include, for example, operation of a range control chart or standard deviation control chart for monitoring the range or standard deviation of a small number of units measured, or criteria for the range of values found in each characterization.

NOTE 1 6.15 provides additional guidance regarding reliance on experience gained from previous production batches.

NOTE 2 ISO 7870-2[73] gives guidance on the use of range control charts and standard deviation control charts.

7.3 Properties to be studied

Where homogeneity is to be determined experimentally it is usually necessary to determine the homogeneity for every property of interest, that is, every property for which the material is claimed to be sufficiently homogeneous for the intended use.

The homogeneity of all properties of interest may be assessed by examining a smaller number of selected properties when

— there is sufficiently high statistical correlation between particular property values in the type of material of interest to allow useful prediction of one property value from one or more others, and

— it can be shown that particular groups of properties are sufficiently closely associated (for example, because of their presence in a particular component of a mixture) that measurement of one property in such a group furnishes evidence of homogeneity for other properties in the same group.

It is essential that any subset of properties taken as representing homogeneity for a larger set of properties be appropriately selected on the basis of established chemical or physical relationships. For example, an inter-element concomitance in the mineral phases of an RM would support the assumption that the RM also has a similar degree of homogeneity for the non-selected elements.

In cases where homogeneity is assessed experimentally by using a subset of properties of interest, additional evidence should be gained about the homogeneity of properties that are not studied experimentally. The evidence should be sufficient to show that the uncertainty associated with heterogeneity is not underestimated for those properties that are not experimentally studied.

NOTE Such evidence can be gained, for example, from literature relevant to the material in question, through the stability study or the characterization of the material.

7.4 Statistically valid sampling schemes

7.4.1 Minimum number of units for a homogeneity study

7.4.1.1 Homogeneity study for quantitative properties

Homogeneity studies for quantitative properties are typically intended to provide information on the variance due to heterogeneity and on any (possibly nonlinear) trends arising from processing. To achieve these objectives, the number of items should be sufficient to give a reasonable estimate of the between-unit variance, and sufficient items taken to give a clear view of any trends present.

Based on current practice, an acceptable estimate of the between-unit variance for the purposes of uncertainty evaluation can be obtained with nine or more degrees of freedom. For a simple