GUIDE 35

Reference materials — General and statistical principles for certification

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

Draft Guides adopted by the responsible Committee or Group are circulated to the member bodies for voting. Publication as a Guide requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO Guide 35 was prepared by the ISO *Reference Materials Committee* (REMCO).

This third edition cancels and replaces the second edition (ISO Guide 35:1989), of which all clauses referring to the estimation of measurement uncertainty have been thoroughly revised. This revision also provides an up-to-date description of the technical issues related to the production and certification of reference materials.

Introduction

The production, characterization and certification of reference materials (RMs) is a key activity in improving and maintaining a worldwide coherent system of measurements. As detailed in ISO Guide 32 and ISO Guide 33, certified reference materials (CRMs) are used for calibration, quality control and method validation purposes, as well as for the assignment of values to other materials, which in turn can also be CRMs. Furthermore, CRMs are used to maintain or establish traceability to conventional scales, such as the octane number, hardness scales and pH. Last, but not least, selected pure substances are also used to maintain the international temperature scale.

For producers of CRMs, there are three ISO Guides that assist the set-up of a facility to produce and certify RMs and to ensure that the quality of thus-produced CRMs meet the requirements of the end-users. ISO Guide 34 outlines the requirements to be met by a CRM producer to demonstrate competence, whereas this Guide provides assistance on how to meet these requirements. At a fairly generic level, this Guide provides models for homogeneity testing, stability testing, and the characterization of the candidate CRM. ISO Guide 31 describes the format and contents of certificates for CRMs.

In some ways, this Guide can be seen as an application of the *Guide to the Expression of Uncertainty in Measurement* (GUM) with respect to the peculiarities of the production of CRMs. Where possible, this Guide makes reference to the GUM, as the latter describes in detail how to evaluate measurement uncertainty of a value obtained from measurement. This Guide complements the GUM in a sense that it provides additional guidance with respect to the inclusion of the uncertainties due to the (remaining) batch inhomogeneity and instability of the CRM in the uncertainty of the property values, and the determination of these uncertainty contributions.

Although this Guide has been developed to support best practice in the production and characterization of RMs, using it without carefully considering whether specific parts are applicable to the particular CRM may still cause its property values (and their uncertainties) to be established on a wrong or faulty basis. A user of this type of documentation should consider that it cannot substitute for "critical thinking, intellectual honesty and professional skill" (GUM:1993, 3.4.8). The quality of the "product" CRM depends as much on these aspects as on the use of proper procedures and methods.

Thorough knowledge of the material and its properties, and of the measurement methods used during homogeneity testing, stability testing and characterization of the material, along with a thorough knowledge of the statistical methods, are needed for correct processing and interpretation of experimental data in a typical certification project. It is the combination of these required skills that makes the production and certification of RMs so complex. The greatest challenge in these projects is to combine these skills to allow a smooth implementation of the project plan.

Most of the contents of this Guide can be applicable to the production of RMs. Requirements such as the traceability of the property values, the necessity of a full evaluation of measurement uncertainty, among others, apply to most categories of RMs to serve, for example, as calibrants or as a means to check the performance of a method, or to assign a value to another material.

Pharmacopoeial standards and substances are established and distributed by pharmacopoeial authorities following the general principles of this Guide. Specific guidance for the production of these kinds of RMs exists. It should be noted, however, that a different approach is used by the pharmacopoeial authorities to give the user the information provided by certificates of analysis and expiration dates. Also, the uncertainty of their assigned values is not stated since it is not permitted by the prescribed use of these RMs in the relevant compendia.

Reference materials — General and statistical principles for certification

1 Scope

This Guide gives statistical principles to assist in the understanding and development of valid methods to assign values to properties of a reference material, including the evaluation of their associated uncertainty, and establish their metrological traceability. Reference materials (RMs) that undergo all steps described in this Guide are usually accompanied by a certificate and called a certified reference material (CRM). This Guide will be useful in establishing the full potential of CRMs as aids to ensure the comparability, accuracy and compatibility of measurement results on a national or international scale.

In order to be comparable across borders and over time, measurements need 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 materials and/or samples. 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 SI units or other internationally agreed units during production. This Guide explains how methods can be developed that will lead to well established property values, which are made traceable to appropriate stated references. It covers a very wide range of materials (matrices), ranging from gas mixtures to biological materials, and a very wide range of properties, ranging from chemical composition to physical and immunoassay properties.

The approaches described in this Guide are not intended to be comprehensive in every respect of the production of an RM and the establishment of its property values, including the associated uncertainties. The approaches given in this Guide can be regarded as mainstream approaches for the production and value assignment of large groups of RMs, but appropriate amendments can be needed in a particular case. The statistical methods described exemplify the outlined approaches, and assume, e.g., normally distributed data. In particular when data are definitely not normally distributed, other statistical methods may be preferred to obtain valid property values and associated uncertainties. This Guide describes in general terms the design of projects to produce a CRM.

2 Normative references

The following referenced documents are indispensable for the application 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 3534-1, *Statistics — Vocabulary and symbols — Part 1: Probability and general statistical terms*

ISO Guide 30, *Terms and definitions used in connection with reference materials*

Guide to the expression of uncertainty in measurement. BIPM, IEC, IFCC, ISO, IUPAC, IUPAP, OIML, 1993 [1)]

1) This edition was corrected and reprinted in 1995.

International vocabulary of basic and general terms in metrology. BIPM, IEC, IFCC, ISO, IUPAC, IUPAP, OIML, 1993

NOTE The "Guide to the expression of uncertainty in measurement" will hereafter be referred to as "GUM", whereas the "International vocabulary of basic and general terms in metrology" will be referred to as "VIM".

3 Terms, definitions and symbols

For the purposes of this document, the terms and definitions given in ISO 3534-1, ISO Guide 30 and VIM, together with the following, apply. The symbols to be used are given in Clause 4.

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 RM is a generic term.

NOTE 2 Properties can be quantitative or qualitative (e.g. identity of substances or species).

NOTE 3 Uses can include the calibration of a measurement system, assessment of a measurement procedure, assigning values to other materials, and quality control.

NOTE 4 An RM can only be used for a single purpose in a given measurement.

3.2
certified reference material
CRM
reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability

NOTE 1 The concept of value includes qualitative attributes such as identity or sequence. Uncertainties for such attributes may be expressed as probabilities.

NOTE 2 Metrologically valid procedures for the production and certification of reference materials are given in, among others, ISO Guide 34 and this Guide.

NOTE 3 ISO Guide 31 gives guidance on the contents of certificates.

3.3
property value
⟨of a reference material⟩ value attributed to a quantity representing a physical, chemical or biological property of a (certified) reference material

3.4
characterization
⟨of a reference material⟩ process of determining the property values of a reference material, as part of the certification process

NOTE 1 The characterization process provides the values for the properties to be quantified.

NOTE 2 In batch certifications, the characterization refers to the property values of the batch.

3.5
between-bottle homogeneity
bottle-to-bottle variation of a property of a reference material

NOTE It is understood that the term "between-bottle homogeneity" applies to other types of packages (e.g. vials) and other physical shapes and test pieces.

