



GUIDE 32

Calibration in analytical chemistry and use of certified reference materials

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Foreword

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

ISO Guide 32 was prepared by the ISO Committee on Reference Materials (REMCO).

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Introduction

Within the framework of the International Laboratory Accreditation Conference (ILAC), held in Torino (Italy) in October 1990, a one-day technical seminar was devoted to *Metrology in testing* where the various aspects of metrological traceability in different fields of testing were addressed.

In order to clarify the implementation of the principles of metrological traceability in chemistry, it was then requested that an ILAC Guide be established on *Calibration in analytical chemistry and use of certified reference materials*.

A draft was established which, after amendments by an ILAC Working Group, was approved by the 1992 ILAC Conference in Ottawa (Canada). Moreover, due to a worldwide need for such information, it was further recommended to transmit this draft to ISO/REMCO to serve as basis for development of an ISO Guide. This proposal was accepted by ISO/REMCO.

Finalization of this Guide was carried out by ISO/REMCO Task Group 2, *Calibration*.

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Calibration in analytical chemistry and use of certified reference materials

1 Scope

Quality assurance in a testing laboratory, particularly in the case of its assessment (see ISO/IEC Guide 25), highlights the need to consider closely the question of the accuracy of its measurements and analytical results, and to ensure that the principles necessary to establish demonstrated accuracy have not been omitted.

The calibration of the parameters associated with chemical analyses and material testing deserves particular attention, because major errors can be made by neglecting or ignoring the basic principles of metrology which also apply to these areas. This Guide identifies a number of general recommendations for those who, either in laboratories or as assessors, are faced with this problem.

2 References

ISO/IEC Guide 25:1990, *General requirements for the competence of calibration and testing laboratories*.

ISO Guide 30:1992, *Terms and definitions used in connection with reference materials*.

ISO Guide 31:1981, *Contents of certificates of reference materials*.

ISO Guide 33:1989, *Uses of certified reference materials*.

ISO Guide 34:1996, *Quality system guidelines for the production of reference materials*.

ISO Guide 35:—¹, *Certification of reference materials — General and statistical principles*.

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

Guide to the expression of uncertainty in measurement. 1st edition, 1993 (corrected and reprinted 1995).

3 Basic considerations

Any measurement, particularly any quantitative chemical analysis, shall employ reference elements to ensure demonstrated traceability to the relevant basic quantities. This is an essential condition for the accuracy of the results.

The metrological quality of the calibration performed depends on:

¹ To be published. (Revision of ISO Guide 35:1989)

- the uncertainty of the reference used (set of calibration masses, titrated solutions, gas mixtures, composition CRMs², etc.),
- the appropriateness (or fitness for purpose) of this reference under the practical conditions of use, also taking into account the analytical method used and the tested samples.

The uncertainty of calibration results from these two components, and it has to be optimized without ignoring either of them.

The analyst should compare the uncertainty of calibration with the required uncertainty of the analysis (which, normally, should be agreed between the customer and the operator). This comparison provides a useful guide for choosing between different available calibration procedures and, in the longer term, for improvements to the methods and procedures.

In tests based on measurements of physical quantities, the principle of traceability of the standards and/or measuring instruments of the accredited laboratory to a national primary standard through a national calibration system, is generally applied. Relevant principles for ensuring the traceability of chemical analyses are presented later in this document; the use of CRMs for that purpose has been gaining importance in the last decades and may be expected to develop even more, if and when they are available.

4 Selection of calibration procedures in chemical analysis

4.1 Types of analytical procedures

The first step consists in classifying the analytical procedure used into one of the following categories :

- Type I
- Type II
- Type III

each of these categories being associated with :

- a basic principle
- a number of basic prerequisites.

When the user classifies a method, it should be done by means of a detailed and close examination of all the parameters of the analytical procedure. He/she must never be satisfied with simplifications which would only be applicable to the detection principle applied under idealized conditions. This approach generally results in underestimating the necessary conditions for a reliable calibration and of generating systematic errors.

Calibration does not make an inaccurate method true (e.g. presence of major interferences). The variability of the influencing factors should only cause a negligible variation in the analytical signal.

² Remarks :

- a) The definitions of RMs and CRMs can be found in ISO Guide 30. RMs can also be used to validate methods (see ISO Guide 33). They may also be used to check the drift with time, and possibly to correct an instrumental drift. They also serve as a basis for a conventional scale (e.g. octane index). These aspects of the use of RMs are not dealt with here, apart from a few remarks, and the reader can refer to ISO Guide 33. One can refer also to more general documentation, such as the VIM (*International vocabulary of basic and general terms in metrology*).
- b) The analytical chemist is often a user of analytical materials or reagents. These products shall not be confused with CRMs. In fact, a CRM corresponds to an identified batch of material of which the certified characteristics have been determined with an optimised and defined accuracy. An analytical reagent is only characterised by a nominal value, determined with a large uncertainty. It is the user's duty to observe all necessary precautions to ensure, when used, that an analytical reagent meets his/her needs.

The above classification is merely designed to identify the relevant calibration mode(s). It shall not be used as a scale of value of the methods.

4.1.1 Type I

This method type produces the anticipated result by performing a calculation defined on the basis of the laws governing the physical and chemical parameters involved, using measurements taken during the analysis, such as:

- mass of the test sample, volume of titration reagent,
- mass of precipitate, volume of titration product generated.

4.1.2 Type II

This method type compares the content of the sample to be analysed to a set of calibration samples of known content, using a detection system for which the response (ideally linear) is recognized in the relevant working area (without necessarily being calculable by theory). The value of the sample content is determined by interpolation of the sample signal with respect to the response curve of the calibration samples.

This implies that any other difference in composition, form, etc., between the calibration set and the different samples analysed will have no effect, or a negligible effect compared with the uncertainty, on the signal. For this condition to be satisfied, the analytical procedure could include:

- means to reduce sensitivity to differences (e.g. spectral buffer, treatment of samples before analysis);
- a procedure to give similar form to the calibration set and the samples:
 - reduce the complex sample to a simpler sample, e.g. by acid digestion, the removal of major interferents, or selective extraction of analyte;
 - synthesize a more complex calibration set by multi-element matrix simulation or the use of a special medium (e.g. oils).
- limitation of the field of application.

4.1.3 Type III

For this method type, the sample to be analysed is compared to a set of calibration samples, using a detection system which has to be recognised to be sensitive not only to the content of elements or molecules to be analysed, but also to differences of matrix (of any type whatsoever). If this influence is ignored, it will generate a systematic error (bias).

For this type of method to be really appropriate for use, it is essential:

- to identify the type(s) of samples routinely analysed (type of matrix, type of structure, etc.) and to draw up procedures to identify the introduction of "abnormal" samples in comparison with the identified types,
- to make up a set of CRMs suitable for each type of sample previously identified,
- to evaluate whether or not "intra-type" differences are liable to generate an unacceptable bias in the analysis.

4.2 Other methods

Any analytical method that fails to ensure traceability to the base units of the SI by one of these approaches is liable not to yield results of demonstrated uncertainty. Even if it offers appreciable advantages of repeatability and reproducibility, the results obtained are liable to be distorted by a systematic error.

If such an analytical method is used by a single laboratory to analyse drift, or to transfer information within a restricted circle of users who are aware of the limitations of the result, vigilance will be necessary to ensure that these results are not presented or used as accurate outside the circle.

Assessors giving accreditation to such methods should take great care to check that the method is undertaken in such a way that appropriate accuracy is ensured through relevant procedures and means, and preferably that they are widely recognized as state-of-the-art methods.

5 Calibration procedures

5.1 Type I method

The basic procedure is to identify every quantity whose measurement is necessary to establish the analytical result by calculation.

It is recommended that a "provisional list of uncertainties" be drawn up which will evaluate the uncertainty of each measured quantity, keeping in mind the required uncertainty of the calibration. This will help to identify the main sources of uncertainty and to exercise special care in selecting the calibration procedures.

With this type of method, CRMs are used for validation (see ISO Guide 33). Note that the CRM shall be analysed as presumed unknown, the result obtained being compared with the certified value. If an abnormal deviation is observed, the laboratory needs to identify the cause and correct it. It is not recommended (except for very specific cases) to deduce a correction factor for the difference between the value found and the certified value.

5.2 Type II method

For this type of method, the working standards generally consist of a determined quantity of analyte "diluted" in a larger quantity of "diluent". They are obtained by measuring the masses or volumes of the different pure, diluted and diluent materials.

Depending on each case, metrological traceability implies the following.

- Calibration of the mass measurements, by calibration or verification of the balances and/or calibration of the volume measurement system.
- Calibration of the system for measuring the correction parameters applied to the foregoing measurements (e.g. temperature, pressure, relative humidity). Since the uncertainties of these quantities are generally of the second order with respect to the total analytical uncertainty, a simplified calibration procedure is often adequate.
- Knowledge of the purity of the basic materials used, together with their uncertainties.

For the substance which is diluted, it is necessary to ensure that :

- it is the compound of interest,
- the nature of the impurities is identified (e.g. inorganics in an organic substance),
- the stoichiometry is correct.

For "diluent", particular attention shall be paid to the residual level of impurities such as:

- the substance to be diluted,
- any substance exhibiting a similar analytical response,
- any substance likely to react with the substance being diluted.

For practical or economic reasons, laboratories may decide to use commercial standard solutions. If so, it is important to make sure that the uncertainty on their content is known, as required, and that the basic rules set forth above are complied with by the manufacturer, as attested by appropriate documentation.

For this type of method, CRMs are chiefly used as a means of validation.

CRMs are sometimes used to prepare a calibration solution by simple dissolution of a known test sample of CRM. This practice is comparable to that of using commercial standard solutions and shall be treated as such.

5.3 Type III method

Since these methods are sensitive to matrix effects, the calibration procedures employed shall take into account these effects. The use of an appropriate CRM is the preferable calibration method. The choice of the CRM to be used has, therefore, to satisfy two types of necessary condition:

- that the certified property is known with sufficient reliability
- that the matrix of the standard is sufficiently similar to the samples being analysed, and that the existing differences are not liable to generate a bias in the results that is incompatible with the required uncertainty of the calibration.

The selection of a suitable CRM should aim to achieve an optimum between these two types of necessity.

The CRM shall initially be defined in the form of a tentative specification; the points to be considered include:

- What are the elements whose concentrations need to be known to permit the establishment of the calibration? Over what concentration range? With what uncertainty? For what sample size?
- What should be the type of matrix: type of material and main components (which could have a "chemical" or "physical" influence on the response of the analyser)?
- What other properties or characteristics of the samples and the standards should be similar to avoid generating a bias in the responses of the analyser? For example: form, viscosity, particle-size distribution, metallurgical structure, etc.

5.4 General remarks

Calibration is an integral part of analysis and its cost is an integral part of the cost of analysis. It shall be planned and provided for, especially if it involves purchasing CRMs or developing internal RMs. An underestimation of these costs does not justify an inadequate calibration procedure.

The calibration of chemical analyses shall meet a number of essential requirements, such as those set forth in this Guide. Compliance with such requirements may involve different forms in different fields. These general recommendations are not sufficient conditions for quality in calibration. Every user, therefore, needs to indicate :

- his/her additional specific conditions,
- any exception to the general rules.

At all events, he/she shall identify and analyse his/her need in its different aspects, and draw up and implement a response for each.

An accurate analysis depends not only on the metrological quality of the calibration, but also on other factors, including random and systematic errors which occur during the analysis.

6 Selection of CRMs

The first approach in this search is to compare the tentative specification of the CRM required with the lists of CRMs available on the international market. The laboratory should consult:

- the catalogues of the different manufacturers
- the COMAR data bank
- if available, branch publications or recommendations examining the best choices of CRM in a specific field
- the recommendations of ISO Guide 34.

The laboratory shall ensure that the CRMs that were short-listed after a first examination:

- are effectively certified for the element concerned, and that the value is not merely indicative (see certificate)
- that the certification procedure exhibits an appropriate level of metrological reliability (see ISO Guide 35), and that it is sufficiently well documented (ISO Guide 31). Any traceability defined in principle only, but without an evaluation of the uncertainty, does not constitute a properly demonstrated traceability.

As to the similarity of matrix, the laboratory shall weigh the fact that it is neither economically nor technically possible, in all cases, to obtain a perfect match between CRMs and samples. Reasonable similarity shall be deemed acceptable. If not, the entire analytical procedure has to be reconsidered.

The use of a CRM available on the market is usually capable of ensuring :

- the best guarantee of accuracy,
- the best performance/cost ratio.

The laboratory that decides not to use appropriate available CRMs should accordingly justify the reasons for this decision in its procedures.

7 Use of *in-house* RMs

Should the market fail to offer a CRM to meet a laboratory's identified needs, the laboratory may attempt to develop its own *in-house* RM. Since this usually means a lengthy and costly operation, involving the use of special resources and experience, it would be wise to first explore the following possibilities.

- Contact those manufacturer(s) of CRMs capable of developing such a new CRM. A request for a new CRM for which the potential market would not amount to more than several dozen per year over several years cannot normally be considered.

- Contact groups of users with the same need and try to set up a joint project, possibly with the assistance of the national laboratory responsible for CRMs.

The preparation and use of an *in-house* RM shall offer guarantees and documented evidence of metrological traceability. A level of accuracy lower than a CRM is justified by better fitness for purpose or imposed by the absence of CRM.

An *in-house* RM shall be prepared by a procedure that guarantees the following:

- sufficient availability over several years;
- demonstrated homogeneity and stability;
- an internal certification analysis assuring demonstrated traceability and ensuring the absence of bias which might have an adverse effect on the required uncertainty of the calibration;
- a quantified uncertainty that fulfills the required uncertainty of the calibration; for the characterization of an internal RM, this requirement usually entails the application of type I or type II methods, preferably validated by the use of CRMs.

In some cases, an *in-house* RM is developed to help conserve an expensive CRM. It can be calibrated (against a set of similar CRM) using a type III method. As this new link will increase the uncertainty of the working RM, the use of such RMs shall be seriously assessed.

Internal RMs shall never be samples of which the reference value used is not known through a procedure of demonstrated traceability with a definite and sufficient uncertainty. If the development of an *in-house* RM necessary to properly calibrate a given method is not technically or economically feasible, the user will have to reconsider the choice of method and/or procedure, and use one that does not demand the missing CRM.