GUIDE 34

General requirements for the competence of reference material producers

Second edition 2000

PDF disclaimer

This PDF file may contain embedded typefaces. In accordance with Adobe's licensing policy, this file may be printed or viewed but shall not be edited unless the typefaces which are embedded are licensed to and installed on the computer performing the editing. In downloading this file, parties accept therein the responsibility of not infringing Adobe's licensing policy. The ISO Central Secretariat accepts no liability in this area.

Adobe is a trademark of Adobe Systems Incorporated.

Details of the software products used to create this PDF file can be found in the General Info relative to the file; the PDF-creation parameters were optimized for printing. Every care has been taken to ensure that the file is suitable for use by ISO member bodies. In the unlikely event that a problem relating to it is found, please inform the Central Secretariat at the address given below.

ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 734 10 79
E-mail copyright@iso.ch
Web www.iso.ch

Printed in Switzerland

Contents

Page

Foreword

ISO (the International Organization for Standardization) and IEC (the International Electrotechnical Commission) form the specialized system for worldwide standardization. National bodies that are members of ISO or IEC participate in the development of International Standards through technical committees established by the respective organization to deal with particular fields of technical activity. ISO and IEC technical committees collaborate in fields of mutual interest. Other international organizations, governmental and non-governmental, in liaison with ISO and IEC, also take part in the work.

Guides are drafted in accordance with the rules given in the ISO/IEC Directives, Part 3.

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.

Attention is drawn to the possibility that some of the elements of this Guide may be the subject of patent rights. ISO and IEC shall not be held responsible for identifying any or all such patent rights.

ISO Guide 34 was prepared by the ISO Committee on Reference Materials (REMCO).

This second edition cancels and replaces the first edition (ISO Guide 34:1996), which has been technically revised.

Annex A of this Guide is for information only.

Introduction

The use of reference materials makes possible the transfer of the values of measured or assigned quantities between testing, analytical and measurement laboratories. Such materials are widely used for the calibration of measuring equipment and for the evaluation or validation of measurement procedures. In certain cases, they enable properties to be expressed conveniently in arbitrary units.

There is an increasing number of reference material producers, and a demonstration of their scientific and technical competence is now a basic requirement for ensuring the quality of reference materials. The demand for new reference materials of higher quality is increasing as a consequence of both the increased precision of measuring equipment and the requirement for more accurate and reliable data in the scientific and technological disciplines. Some previously acceptable reference materials may not meet these more stringent requirements. It is, therefore, not only necessary for reference material producers to supply information about their materials in the form of reports, certificates and statements, but also to demonstrate their competence in producing reference materials of appropriate quality.

The first edition of ISO Guide 34 set out specific guidelines on the interpretation of ISO/IEC Guide 25 and the ISO 9000 family of standards in the context of reference materials production. The more general requirements of these standards were omitted. Since the first edition of ISO Guide 34 was published in 1996, the assessment of the competence of reference material producers has gained considerable impetus. The present revision of Guide 34 now sets out all the general requirements in accordance with which a reference material producer has to demonstrate that it operates.

Pharmacopoeial standards and substances are established and distributed by pharmacopoeial authorities following the general principles of this Guide. 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 negligible in relation to the defined limits of the method-specific assays of the pharmacopoeias for which they are used.

General requirements for the competence of reference material producers

1 Scope

1.1 This Guide sets out the general requirements in accordance with which a reference material producer has to demonstrate that it operates, if it is to be recognized as competent to carry out the production of reference materials.

1.2 This Guide is intended for the use of reference material producers in the development and implementation of their quality system, and by accreditation bodies, certification bodies and others concerned with assessing the competence of reference material producers.

1.3 This Guide sets out the quality system requirements in accordance with which reference materials shall be produced. It is intended to be used as part of a reference material producer's general quality assurance (QA) procedures.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this Guide. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this Guide are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO/IEC Guide 2:1996, *Standardization and related activities — General vocabulary.*

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 35:1989, *Certification of reference materials — General and statistical principles.*

ISO 8402:1994, *Quality management and quality assurance — Vocabulary.*

ISO 10012-1:1992, *Quality assurance requirements for measuring equipment — Part 1: Metrological confirmation system requirements for measuring equipment.*

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

3 Terms and definitions

For the purposes of this Guide, the terms and definitions given in ISO/IEC Guide 2, ISO/IEC Guide 25, ISO Guide 30, ISO 8402, VIM and the following apply.

3.1
reference material producer
technically competent body (organization or firm, public or private) that is fully responsible for assigning the certified or other property values of the reference materials it produces and supplies which have been produced in accordance with ISO Guides 31 and 35

3.2
collaborator
technically competent body (organization or firm, public or private) that undertakes aspects of the manufacture or characterization of the (certified) reference material on behalf of the reference material producer, either on a contractual (as a subcontractor) or voluntary basis

4 Organization and management requirements

4.1 Quality system requirements

4.1.1 General

The reference material producer shall establish, implement and maintain a quality system appropriate to the scope of its activities, including the type, range and magnitude of the reference material production it undertakes.

It should be recognized that a reference material needs to be characterized mainly to the level of accuracy required for its intended purpose (i.e. appropriate measurement uncertainty). The reference material producer shall describe the procedure for establishing the quality of materials as a component of the quality system.

Reference material producers shall define their scope in terms of the application, the measurement methods used in the homogeneity, stability and characterization studies, and any limitations due to the material matrix.

4.1.2 Quality policy

The reference material producer shall define and document its policy, objectives and commitment to ensuring and maintaining the quality of all aspects of reference material production, including material quality (e.g. homogeneity and stability), characterization (e.g. equipment calibration and measurement method validation), assignment of property values (e.g. use of appropriate statistical procedures) and material handling, storage and transport procedures.

The quality policy shall, when appropriate, include use of interlaboratory characterization studies employing laboratories which are active and competent in the respective field of measurement. In this context, the policy shall include a commitment to interact with the appropriate sectors of the measurement community, in order to prevent working in isolation. The policy shall also include a commitment to produce reference materials which conform to the definitions given in ISO Guide 30, characterized according to the requirements of ISO Guide 35 and whose property values are assessed using accepted statistical techniques. The policy shall, where appropriate, include a commitment to comply with ISO Guide 31 for the contents of reference material certificates and supply of associated information for users. It is important that the policy also specify the intended use of the reference materials, in order to ensure that the reference material producer fully advises the user for which types of application the materials may be used.

4.1.3 Quality system

The reference material producer shall establish, implement and maintain a documented quality system appropriate to the type, range and volume of reference material production it undertakes. The reference material producer shall document all of its policies, systems, programmes, procedures, instructions, findings, etc., to the extent necessary

to enable the producer to assure the quality of the reference materials produced. Documentation used in this quality system shall be communicated to, understood by, available to and implemented by all personnel concerned. In particular, the producer shall have a quality system that covers the following:

a) arrangements for ensuring the suitable choice (e.g. particle size range, concentration range, etc.) of the candidate reference materials;

b) preparation procedures;

c) achievement of the required degree of homogeneity of the reference material;

d) assessment of the stability of the reference material; including on-going assessment of stability where necessary;

e) procedures for undertaking characterization;

f) practical realization of traceability to national or international standards of measurement;

g) assignment of property values, including preparation of certificates or statements in accordance with ISO Guide 31 when appropriate;

h) arrangements for ensuring adequate storage facilities;

i) arrangements for suitable identification, labelling and packaging facilities, packing and delivery procedures and customer service;

j) compliance with ISO Guides 30, 31, 34 and 35.

The documented quality system should specify which activities are undertaken by the reference material producer and, where relevant, which activities are undertaken by collaborators. It shall include policies and procedures used by the producer to ensure that all activities conducted by collaborators comply with the relevant clauses of this Guide.

The documented quality system shall define the roles and responsibilities of the technical manager (however named) and quality manager, including their responsibilities for ensuring compliance with this Guide.

4.2 Organization and management

4.2.1 The reference material producer, or the organization of which it is part, shall be legally identifiable.

4.2.2 The reference material producer shall be organized and shall operate in such a way that it meets all the applicable requirements of this Guide, whether carrying out work in its permanent facilities or at sites (including associated temporary or mobile facilities) away from its permanent facilities (including work undertaken by collaborators).

4.2.3 The reference material producer shall:

a) have managerial personnel supported by technical personnel with the authority and resources needed to discharge their duties and to identify the occurrence of departures from the quality system or the procedures for the production of reference materials and to initiate actions to prevent or minimize such departures;

b) have arrangements to ensure that its management and personnel are free from any commercial, financial and other internal and external pressures that may adversely affect the quality of their work;

c) have policies and procedures to ensure the protection of its client's confidential information and proprietary rights;

d) have policies and procedures to avoid involvement in any activities that might diminish confidence in its competence, impartiality, judgement or operational integrity;

e) define, with the aid of organizational charts, the organization and management structure of the reference material producer, its place in any parent organization, and the relations between management, technical operations, support services, collaborators and the quality management system;

f) specify the responsibility, authority and interrelationships of all personnel who manage, perform or verify work affecting the quality of production of reference materials;

g) have technical management, which has overall responsibility for the technical operations and the provision of the resources needed to ensure the required quality of each operation which forms part of the reference material production;

h) appoint a member of staff as quality manager (however named) who, irrespective of other duties and responsibilities, shall have defined responsibility and authority for ensuring that the requirements of this Guide are implemented and followed at all times. The quality manager shall have direct access to the highest level of management at which decisions are taken on production policy or resources;

i) where appropriate, appoint deputies for key managerial personnel such as the technical and quality managers.

4.3 Document and information control

4.3.1 General

The reference material producer shall establish and maintain procedures to control all documents (both internally generated and from external sources) and other information that form part of its quality documentation. These may include documents of external origin, such as standards, guides, test and/or calibration methods, as well as specifications, instructions and manuals related to the reference material under production.

NOTE In this context “document” means any information or instruction including policy statements, text books, procedures, specifications, calibration tables, charts, software, etc. These may be on various media, whether hard or electronic, and they may be digital, analog, photographic or written.

4.3.2 Document approval and issue

4.3.2.1 All documents (including documented procedures) issued to personnel as part of the quality system shall be suitably controlled. This shall include review and approval for use by authorized personnel prior to issue. A master list or equivalent, identifying the current revision status of documents in the quality system, shall be established and be readily available to preclude the use of invalid and/or obsolete documents.

4.3.2.2 The procedures adopted shall also ensure that:

a) authorized editions of appropriate documents are available at all locations where operations essential to the effective production of reference materials are performed;

b) documents are periodically reviewed and, where necessary, revised to ensure continuing suitability and compliance with applicable requirements;

c) invalid or obsolete documents are promptly removed from all points of issue or use, or otherwise assured against unintended use;

d) obsolete documents retained for either legal or information preservation purposes are suitably marked.

4.3.3 Document changes

4.3.3.1 Changes to documents (including documented procedures) shall be reviewed and approved by designated personnel performing the same function as that conducted for the original review and approval unless specifically decided otherwise. The designated personnel shall have access to pertinent background information upon which to base their review and approval.

4.3.3.2 Where practicable, the nature of the change shall be identified in the document with appropriate attachments.

4.3.3.3 If the reference material producer's documentation control system allows for the amendment of documents by hand, pending the re-issue of the documents, the procedures and authorities for such amendments shall be defined and shall ensure that amendments are initialled and dated. Documents amended by hand shall be marked, signed and dated and shall be formally re-issued as soon as practicable.

4.3.3.4 Procedures shall be established to describe how changes in documents maintained in computerized systems are made.

4.4 Request, tender and contract reviews

4.4.1 When relevant, each request, tender or contract concerning the production of a reference material shall be reviewed by the reference material producer to ensure that:

a) the requirements are adequately defined, documented and understood;

b) the reference material producer has the capability and resources to meet the requirements;

c) in the case of external contracts, any differences between the contract or order requirements and those in a tender are resolved to the satisfaction of the reference material producer and the customer or client.

The request, tender or contract review should be conducted in a practical and efficient manner and the financial, legal and time schedule aspects should be taken into account.

NOTE 1 Capability means that the reference material producer possesses the necessary equipment, intellectual and information resources and that its personnel have the skills and expertise necessary for the production of those reference materials in question. The review of the capability may include an assessment of previous reference material production and/or the organization of interlaboratory characterization programmes using samples of similar composition to the reference materials to be produced.

NOTE 2 A contract may be any written or verbal agreement to provide a customer or client with reference materials from stock or custom-produced respectively.

4.4.2 Records of such reviews, including any changes, shall be maintained. Records shall also be maintained of pertinent discussions with a customer relating to the customer's requirements or the results of the work during the period of execution of the contract or request.

4.4.3 The review shall include any work that has to be subcontracted by the reference material producer.

4.5 Use of collaborators

4.5.1 The reference material producer shall establish and maintain procedures to ensure that all tasks performed by collaborators comply with specifications set by the reference material producer for such tasks. The reference material producer shall also ensure that collaborators comply with any clauses of this Guide relevant to the tasks performed by them for the reference material producer.

4.5.2 The reference material producer shall select collaborators on the basis of their ability to meet subcontracted requirements in terms of both their technical competence and any specific quality assurance requirements relevant to their tasks. The technical requirements to be satisfied by collaborators shall be equivalent to the technical requirements specified in clause 5 of this Guide.

4.5.3 The reference material producer shall maintain a register of all collaborators used in the production process, and include a record of any assessments made of their abilities to carry out subcontracted tasks according to the requirements of this Guide.

The reference material producer is always responsible for ensuring that a collaborator is competent. The collaborator should be able to demonstrate compliance with the requirements of this Guide for all subcontracted work.

4.6 Procurement of services and supplies

4.6.1 The reference material producer shall have policies and procedures for the selection of services and supplies that affect the quality of its reference materials.

4.6.2 The reference material producer shall use only those services and supplies that are of adequate specification to ensure the quality of its reference materials.

4.6.3 When no formal approval of the quality of services and supplies is available, the reference material producer shall have procedures to ensure that purchased materials and services comply with specified requirements and records of actions taken shall be maintained.

4.6.4 The reference material producer shall ensure that purchased equipment and consumable materials are not used until they have been inspected, calibrated or otherwise verified as complying with standard specifications or requirements defined in specifications for production, characterization and certification of its reference materials.

4.6.5 The reference material producer shall maintain records of the main suppliers and collaborators from whom it obtains supplies required for the production of reference materials. These records should include any quality assurance approval the suppliers and/or collaborators hold.

4.7 Client feedback

The reference material producer shall have a policy and procedures for the resolution of complaints or other feedback received from its customers or other parties. Records shall be maintained of all complaints and of the investigations and corrective actions taken by the reference material producer.

4.8 Control of non-conforming (poor quality) reference materials

4.8.1 The reference material producer shall have a policy and procedures that shall be implemented when it establishes that any aspect of its production activities do not conform with its own specified production procedures. The policy and procedures shall ensure that:

a) responsibilities and authorities for the management of non-conforming work are designated;

b) the actions, which must be taken when any non-conforming reference materials are identified, are defined, together with a system which ensures they are implemented;

c) an evaluation of the significance of the non-conforming work is made;

d) work is halted and, if appropriate, certificates withheld as necessary;

e) remedial actions are taken within a defined timeframe;

f) where necessary, the results of non-conforming reference materials already distributed to customers are recalled;

g) the responsibility for authorization of the resumption of work is defined.

NOTE The identification of non-conforming reference materials or problems with the quality system or with certification activities can occur at various places within the quality system such as: customer complaints, quality control, checking of consumable materials, staff observations or supervision, certificate checking, management reviews and internal or external audits.

4.8.2 Where the evaluation indicates that the supply of non-conforming reference materials could recur or that there is doubt about the reference material producer's compliance with its own policies and procedures, the corrective action procedures in 4.9 shall be promptly followed to identify the causes of the problem and to eliminate them.

4.9 Corrective action

4.9.1 General

The reference material producer shall establish a policy and procedures and shall designate appropriate authorities for implementing corrective action when non-conforming reference materials or departures from the policies and procedures in the quality system have been identified.

Any corrective action taken to eliminate the causes of non-conformances or other departures shall be to a degree appropriate to the magnitude of the problems and commensurate with the risks encountered.

The reference material producer shall document and implement any required changes to the operational procedures resulting from corrective action investigations.

NOTE A problem with the quality system or with technical operations may be identified through a variety of activities within the quality system, such as control of non-conforming reference materials, internal or external audits, management reviews, feedback from clients or staff observations.

4.9.2 Cause analysis

Corrective action procedures shall include an investigation process to determine the causes of the problem. This is sometimes the most difficult, but the key part in the corrective action procedure.

Often the root cause is not obvious and thus a careful analysis of all potential causes of the problem is required. Potential causes could include, *inter alia*, the nature of the reference material and its specification, methods and procedures used for characterization, staff skills and training, and the materials and equipment (and/or its calibration) used in the production processes.

4.9.3 Corrective actions

The reference material producer shall identify possible causes and potential corrective actions. It shall select the actions most likely to eliminate the problem and to prevent it recurring.

4.9.4 Monitoring of corrective actions

After having implemented the action plans, the reference material producer shall monitor the results to ensure that the actions taken have been effective in overcoming the problems originally identified.

4.9.5 Results

The results of corrective action shall be submitted for management review.

4.10 Preventative action

4.10.1 All operational procedures shall be systematically reviewed at regular intervals to identify any potential sources of non-conformance and any opportunities for improvement, either technical or with the quality system. Action plans shall be developed, implemented and monitored, to reduce the likelihood of occurrence of such non-conformances and to take advantage of the improvement opportunities.

NOTE 1 Preventative action is a pro-active process to identify improvement opportunities, rather than a reaction to the identification of problems or complaints.

NOTE 2 TQM tools such as brainstorming, flowcharting, mind-mapping and parieto charts can assist this process.

4.10.2 After the implementation of the preventative actions, the reference material producer shall monitor the results to establish any reduction in deficiencies or other improvements in this operational area, thereby establishing the effectiveness of the preventative action.

4.10.3 The results of preventative actions shall be submitted for management review.

4.11 Records

4.11.1 General

4.11.1.1 The reference material producer shall establish and maintain procedures for identification, collection, indexing, access, storage, maintenance and disposal of quality and technical records.

a) Quality records

Quality records are records providing objective evidence of the extent of the fulfilment of the requirements for quality or the effectiveness of the operation of the quality system. For example, they include reports from internal audits and management reviews, and corrective and preventative action records.

b) Technical records

Technical records are accumulations of data and information which result from carrying out testing and calibration procedures and which indicate whether specified quality or process parameters are achieved. They include forms, contracts, work sheets, work books, check sheets, control charts/graphs, calibration reports/certificates and papers, reports and certificates to customers and clients.

The reference material producer should ensure that it has recorded such information that might be needed in a future dispute situation.

4.11.1.2 All records shall be legible and shall be stored and retained in such a way that they are readily retrievable, and in facilities that provide a suitable environment to prevent damage, deterioration or loss. Retention times of records shall be established and recorded.

NOTE Records may be in the form of any type of media, such as hard copy or electronic media.

4.11.1.3 All records shall be held secure and, where appropriate, in confidence to the client.

4.11.1.4 The reference material producer shall have procedures to protect electronically-held data at all times and to prevent unauthorized access to, or amendment of, such data.

4.11.2 Records and reports

The reference material producer shall establish and maintain a record system to suit its particular circumstances and to comply with any applicable regulations. The reference material producer shall arrange for all individual measurement observations, appropriate calculations and derived data (e.g. statistical treatments and uncertainty budgets), calibration records and preparation reports to be retained for a defined period beyond which it is no longer probable that they will be referred to, taking into account the period for which the reference material remains valid.

The results of each calibration or measurement (or series of either) carried out by the reference material producer and, where appropriate, its collaborators, shall be reported unambiguously and objectively, in accordance with any instructions in the calibration or measurement methods. The results shall normally be reported in a calibration or measurement report and shall include all information necessary for interpretation of the calibration or measurement results and a summary of the method employed.

This procedure applies to internal reports of the reference material producer and should not be confused with a certificate of analysis or certification report which is supplied with a reference material to the customer or client.

4.12 Internal audits

4.12.1 The reference material producer shall, periodically and in accordance with a predetermined schedule and procedure, conduct internal audits of its activities to verify that its operations continue to comply with the requirements of the quality system and the requirements of this Guide. The internal audit programme shall address all elements of the quality system, including the technical and production activities leading to the finished product (reference material). It is the responsibility of the quality manager to plan and organize audits as required by the schedule and requested by management. Such audits shall be carried out by trained and qualified personnel who are, wherever resources permit, independent of the activity to be audited. Personnel shall not audit their own activities except where it is necessary and it can be demonstrated that an effective audit has been carried out.

The schedule for internal auditing should normally be completed in one year.

4.12.2 When audit findings cast doubt on the effectiveness of the operations or on the correctness or validity of its reference materials, the reference material producer shall take timely corrective action and shall notify, in writing, its customers whose activities may have been adversely affected.

4.12.3 All audit findings and corrective actions that arise from them shall be recorded. The reference material producer's management shall ensure that these actions are discharged within an appropriate and agreed timescale.

4.13 Management reviews

4.13.1 The reference material producer's senior management shall periodically conduct a review of its quality system and production processes to ensure their continuing suitability and effectiveness and to introduce any necessary changes or improvements. The review shall take account of reports from managerial and supervisory personnel, the outcome of recent internal audits, assessments by external bodies, feedback from customers, including complaints and other relevant factors.

A typical period for conducting a management review is once every year. Results should feed into the corporate planning programme and should include the goals, objectives and action plans for the coming year.

4.13.2 Findings from management reviews and the actions that arise from them shall be recorded. The management shall ensure that these actions are discharged within an appropriate and agreed timescale.

5 Technical and production requirements

5.1 Management, staffing and training

5.1.1 The production of reference materials should, where possible, only be undertaken by organizations having experience in the production of the particular type of reference material (or related material), as well as having experience in the measurement of the properties being determined.

The reference material producer and any associated collaborators shall have managerial staff with the necessary authority, resources and technical competence required to discharge their duties. Measurement of the property of interest shall be completed by, or under the supervision of a technically competent manager qualified either in terms of suitable academic qualifications or relevant work experience. The reference material producer's management shall define the minimum levels of qualification and experience necessary for the key posts within its body.

5.1.2 The reference material producer shall have sufficient personnel having the necessary education, training, technical knowledge and experience for their assigned functions.

EXAMPLE A staff member undertaking thermal expansion measurements should have a degree or appropriate level qualification, together with adequate experience in the field working with a more senior scientist making measurements at an equivalent level of accuracy.

5.1.3 The reference material producer shall also ensure that staff receive additional training, when necessary, to ensure competent performance of measurements, operation of equipment and any other activities which affect quality. Where possible, objective measures should be used to assess the attainment of competence during training.

The need to retrain staff periodically should be considered (e.g. the reference material producer should have in place a policy for retraining staff when a method or measurement technique is not in regular use). Staff training and retraining policies should take account of technological change and aim at continuous skill upgrading.

5.1.4 The reference material producer shall maintain an up-to-date record of the training that each staff member has received. These records shall provide evidence that individual staff members have been adequately trained and that their competence to complete particular types of material preparation and measurement has been assessed.

5.2 Collaborators

5.2.1 Where a reference material producer undertakes any part of the procedure for the production or characterization of a reference material on an interlaboratory basis, the producer shall be able to demonstrate that the experience of any collaborator is sufficient, and that the results produced are of the required quality. In assessing the competence of a collaborator, the reference material producer shall require information on the collaborator's knowledge of the subject and details of past experience in the field (e.g. valid results for comparable measurements). In the latter context, the producer may consider distributing materials of a comparable matrix whose property values are well established and at appropriate concentration levels, ranges, etc., prior to distributing any candidate reference material samples. Evidence of collaborators being accredited to ISO/IEC Guide 25 when testing is carried out, or registered to the ISO 9000 series for other activities, is generally appropriate. Evidence of collaborators participating in a relevant proficiency testing scheme and producing acceptable results on well-characterized materials of similar or equivalent nature to that of the reference material may also be considered appropriate. At the limit, the reference material producer may have no laboratory facilities, but shall ensure that all scientific work carried out by collaborators which may contribute to the assignment of the property values of interest is fit for that purpose and in compliance with the above requirements.

5.2.2 The reference material producer shall ensure that all details of the methodology, results and all the performance procedures of any collaborators are available, if required, and that a register/database of all collaborators and their accreditation/quality system/other forms of competence status is maintained.

5.3 Production planning

5.3.1 The reference material producer shall identify and plan those processes which directly affect the quality of reference material production and shall ensure that they are carried out in accordance with specified procedures.

5.3.2 Organizational and technical input of the different collaborators involved shall be identified and the necessary information documented and regularly reviewed. A mechanism (e.g. a management/technical advisory group) shall be established to make recommendations on how to plan the production processes.

NOTE These could include recommendations for production, setting up a monitoring system (to ensure timeliness and quality for each production phase) and having an evaluation procedure to assess the production processes retrospectively.

5.3.3 In planning the production processes, the reference material producer shall have procedures and service facilities, where appropriate, for:

a) material selection (including, where appropriate, sampling);

b) maintaining suitable environments for all aspects of production;

c) material preparation;

d) measuring/testing;

e) calibration/validation of equipment/measurement methods;

f) assessing material homogeneity;

g) assessing material stability;

h) organizing interlaboratory studies with its collaborators;

i) assigning property values based on the results of measurements;

j) producing uncertainty budgets and uncertainty intervals to the assigned property values;

k) ensuring adequate storage facilities and conditions;

l) ensuring adequate packaging facilities;

m) ensuring appropriate transport arrangements;

n) ensuring an adequate post-distribution service.

5.4 Production control

The reference material producer shall identify the verification procedures necessary to ensure the quality of each stage of reference material production, and shall assign adequate resources and personnel for such activities. These activities should include inspection, testing and monitoring of all stages of production.

5.5 Environment

5.5.1 The reference material producer shall ensure that all laboratory accommodation, calibration and measurement areas, material preparation and packaging areas, energy sources, lighting, temperature, pressure and ventilation are such as to facilitate proper material preparation and packaging, as well as proper performance of calibration and measurements.

It is imperative that all possible precautions are taken against possible contamination of the reference material during its production and certification. All reference material production and testing areas, in addition to satisfying requirements for humidity and temperature, should be protected from vibration, airborne dust and microbiological contamination, magnetic fields and electromagnetic radiation (as appropriate). For example, the packaging of a cement material requires conditions of low humidity, while the preparation and characterization of a material in which the content of traces of lead is to be measured requires cleanroom conditions to prevent contamination from airborne lead particulates due to car emissions. Cleanroom conditions may also be required for other types of trace analysis.

5.5.2 The reference material producer shall ensure that all environmental requirements are also met by any collaborator involved in any production process.

5.5.3 Where appropriate to do so, the environment in which these activities are undertaken shall be monitored with appropriately calibrated equipment, controlled and recorded, such that results and processes are not adversely affected.

5.5.4 Appropriate health, safety and environmental protection precautions shall also be implemented where necessary (e.g. when handling pesticides or serum).

5.6 Material handling and storage

5.6.1 In order to avoid any contamination, the reference material producer shall identify, preserve and segregate (i.e. from other chemicals and samples) all candidate materials and reference materials, from the time of preparation through to their distribution to users.

5.6.2 The reference material producer shall ensure adequate packaging of all reference materials (e.g. where appropriate, use air-free, moisture-free or inert-gas packaging) and provide secure storage areas/stock rooms

which prevent damage or deterioration of any item or material between characterization and distribution. Appropriate methods for authorizing dispatch to, and receipt from, such areas should be stipulated.

5.6.3 The condition of all stored/stocked items and materials shall be assessed at appropriate intervals throughout their storage life, in order to detect possible deterioration.

5.6.4 The reference material producer shall control packing and marking processes to the extent necessary to ensure conformity with safety and transport requirements.

NOTE The proper distribution of samples, for example, can present a severe problem for some types of material which require uninterrupted storage in a freezer, or which should not be exposed to X-rays, shocks or vibrations. Most types of chemical material benefit from air-tight packaging to avoid contamination by atmospheric contaminants (e.g. fuel vapours or engine exhaust gases) which may be encountered during transport.

The reference material producer should ensure that the integrity of the reference material is maintained until the seal has been broken, or up to the point when presented for analysis. The producer cannot be held responsible for the material once its seal has been broken. This may require, in some cases, that the reference material be packaged in unit quantities sufficient for a single use.

5.6.5 The reference material label shall be securely attached to the product packaging of an individual reference material unit, and shall be designed to remain legible and intact within the period of validity of the material. The label shall identify the material, the producer, its batch and catalogue numbers, and any other information necessary to enable the material to be uniquely distinguished and referenced, where appropriate, to its statement or certificate.

5.6.6 The reference material producer shall make arrangements to ensure the integrity of each reference material throughout the entire production process. Where contractually specified, this protection shall be extended to include delivery to destination.

5.7 Post-distribution service

5.7.1 The reference material producer shall establish, document and maintain procedures for ensuring that corrective action is undertaken whenever a product is found not to conform to the specified requirements. Any resultant changes (e.g. in procedures or data) should be recorded, and all purchasers of the reference material notified if there is a change to its assigned property values (e.g. as a result of additional measurement studies) within the period of the validity of the material.

5.7.2 The reference material producer should also provide an advisory service to offer guidance (including a complaints procedure) and technical services to users. Where the goods are subject to resale through a distributor, the reference material producer should make arrangements with the distributor to keep records of purchasers of the reference materials.

5.8 Material preparation

5.8.1 The reference material producer shall establish whether the item or material has received adequate preparation for its intended use. Procedures for material preparation should include, where appropriate:

a) qualitative analysis for verification of material type;

b) machining, grinding, blending, sieving and riffling (i.e. dividing into representative samples);

c) determination of particle size distribution;

d) cleaning of sample containers;

e) drying (including lyophilization) and sterilization;

f) packaging (e.g. bottling, etc.) representative samples from the batch;

g) homogeneity testing;

h) stability testing over a range of conditions which may affect the property values and/or matrix composition of the reference materials being produced (e.g. different levels of humidity, temperature, light, magnetic fields, etc.).

5.8.2 The reference material producer shall be able to demonstrate that the candidate reference material is sufficiently homogeneous; i.e. the difference, if any, between units shall be smaller than the uncertainty limits stated in the certificate.

NOTE A relatively inhomogeneous material may be the best available, and may therefore still be useful as a reference material, provided the uncertainties of the assigned property values take due account of this.

5.9 Assessment of homogeneity and stability

5.9.1 Where appropriate, the reference material producer shall carry out an assessment of the homogeneity of any candidate reference material by analysing a representative number of randomly, systematically or stratified randomly chosen units. This should be done by means of a measurement method, the repeatability of which is fit for the purpose required (i.e. good enough to not contribute significantly to the combined uncertainty). The assessment procedure shall be documented and conducted in accordance with acceptable statistical procedures.

NOTE For reference materials that are expected to be homogeneous on physical grounds, the main purpose of homogeneity testing is to detect unforeseen problems, for example differential contamination during packaging into individual units, or incomplete dissolution or equilibration of an analyte in a solvent (which could lead to steadily changing concentrations). For these types of examples, systematic sampling (e.g. one from every 50 samples produced in a continuous process; sampling at regular intervals for each sub-batch in those cases where the sub-batch can be defined) may often be a better way to detect inhomogeneity than random sampling (e.g. segregation of fine/coarse particles in a powder). A statistical trend analysis may also be helpful in detecting inhomogeneity. If the material is produced in several batches, it will be necessary to test the equivalence of the batches (or to assign property values to each batch separately). The assessment should be performed after the material has been packaged in its final form unless stability studies indicate that storage should be maintained in bulk form. In some cases, an intermediate homogeneity check may be necessary (e.g. prior to ampouling).

5.9.2 Where appropriate, the property values to be assessed should be measured periodically, ideally over a range of conditions under which the material is to be stored prior to distribution to the user. The effects of light, moisture, heat and time shall be quantified in order to provide advice on storage location and lifespan (and hence a suitable shelf-life/expiry date).

Stability testing can only be performed after sufficient homogeneity has been demonstrated. Then any sample (assuming that it is not smaller than the samples used to test homogeneity) can be considered representative; there is no constraint on the number of samples required, nor any requirement to choose them randomly. However, results will vary depending on the repeatability and intermediate precision measure of the technique and so replicate tests should be performed.

When use of a reference material is intended for the calibration of a method requiring a small quantity of test sample [e.g. graphite furnace AAS or ICP-OES)], it is necessary to assess the homogeneity on sample sizes of only several hundred micrograms to a few milligrams.

5.9.3 The size of sample on which the homogeneity of the reference material has been established shall be specified on the documentation supplied by the reference material producer. This documentation should also state the minimum sample size for use.

5.9.4 Where appropriate, an assessment of the stability of the assigned property values of the reference material performed at periodic intervals after characterization to confirm that all values are maintained from production until its expiry date. Wherever appropriate, the reference material producer shall provide an expiry date for the usable life of the reference materials produced, based on initial and on-going stability studies in compliance with ISO Guide 35. It should be made clear on the certificate of analysis on what criterion the expiry date is based (e.g. the date of certification, the date of shipment or the date of opening the packaging).

NOTE Some certificates may have more than one expiry date, for example a date from certification or a date from opening the container by the user.

5.9.5 The reference material producer shall provide details of the homogeneity and stability studies carried out in accordance with the requirements of ISO Guides 31 and 35.

5.10 Measurement methods

5.10.1 The reference material producer and its collaborators shall use appropriate documented methods or procedures, which include protocols defining approaches to be adopted for different analyses, calibrations, measurements and related activities within their responsibility (including preparation of items, sampling, handling, preservation, storage, packaging, transport to collaborators, estimation of measurement uncertainty and analysis of measurement data). These activities should be consistent with the required accuracy, where appropriate, of the reference material, and with any standard specifications relevant to the measurement concerned.

5.10.2 Measurement methods developed in-house by the reference material producer, or by any collaborators, shall be validated and authorized (e.g. by a management/technical advisory group or appropriately defined person) before use. Such methods shall be thoroughly investigated, and shall clearly and exactly describe the necessary conditions and procedures for which the measurement of the property values of interest are valid at the level of accuracy commensurate with the intended use of the reference material.

NOTE In some cases, reference materials are characterized for method-dependent properties (e.g. leachable metals, pH or flashpoint).

5.10.3 Where sampling is carried out as part of the measurement method (e.g. sub-sampling a representative quantity from a batch of material), the reference material producer shall use documented procedures and appropriate statistical techniques to take test portions.

5.11 Measuring equipment

5.11.1 Measuring equipment used in reference material production shall be properly calibrated or verified and maintained, with all procedures being documented and the results recorded. Where appropriate, periodic performance checks should be carried out (e.g. to check the response, stability, linearity, resolution, alignment, repeatability and separating efficiency) to ensure that the measuring equipment is performing adequately. The frequency of such performance checks shall be determined by experience and based on the type and previous performance of the equipment. Intervals between checks shall be shorter than the time within which the equipment has been found to drift outside acceptable limits, in accordance with the requirements of ISO 10012-1.

5.11.2 Any item of equipment that has been subjected to overloading or mishandling, shown to provide suspect results, or shown by verification or otherwise to be defective, shall be clearly identified, withdrawn from service and, wherever possible, stored at a specified location until repaired and shown by calibration, verification or test to perform satisfactorily. The reference material producer shall review the implications for results obtained using such equipment, with particular regard to the extent of the calibration deviation, the results involved and the allowable tolerance on the results. Where results have been significantly in error, the reference material producer shall have the results checked and shall take appropriate remedial action. Records of the review and any checks/remedial action shall be maintained.

5.11.3 Each item of equipment, including any measurement standard, that is used in the calibration/validation of equipment/measurement methods used for reference material production shall, when appropriate, be labelled, marked or otherwise identified to indicate its calibration status and expiry date. This shall also include reagents used in chemical analysis, microbiological testing, etc.

5.11.4 All measuring and testing equipment having an effect on the accuracy or validity of calibrations or measurements shall be calibrated and/or verified before being commissioned into service. The reference material producer and its collaborators shall have an established programme for the calibration and verification of measuring and test equipment.

5.11.5 The overall programme of calibration and/or verification of equipment shall be designed and operated so as to ensure that, wherever applicable, measurements made by the reference material producer are traceable to

national and/or international standards of measurement through an unbroken chain of comparisons with stated uncertainties. Calibration certificates of measurement instruments shall, wherever appropriate, indicate the traceability to national standards of measurement and shall provide the measurement results and associated uncertainty of measurement.

5.12 Traceability and validation

5.12.1 Where traceability can be related to stated references (usually national or international standards of measurement) through an unbroken chain of comparisons, all having stated uncertainties, the reference material producer and its collaborators shall provide documentary evidence of the traceability of measurements.

5.12.2 Where this cannot be achieved, the reference material producer shall provide satisfactory evidence of the correlation of results with other stated values, either by exhaustive evaluation of the measurement process or by correlation with known and accepted national and/or international certified reference materials.

NOTE A more complete discussion on the concept and requirements of traceability is given in annex A.

5.13 Data evaluation

5.13.1 The reference material producer shall ensure that calculations and data transfers are subject to appropriate checks, including those from its own sources or, where appropriate, those from its collaborators.

5.13.2 Where computers/computers-controlled systems are used for the capture, processing, evaluation, recording, reporting, storage or retrieval of calibration or test data, the reference material producer shall ensure that, for itself and collaborators:

a) computer software is validated wherever possible, especially when developed in-house, and is adequate for use;

b) procedures are established and implemented for protecting the integrity of data; such procedures should include, but are not limited to, integrity of data entry and capture, data storage, data transmission and data processing;

c) equipment is maintained to ensure proper functioning and is provided with the environmental and operating conditions necessary to maintain data integrity;

d) appropriate procedures are established and implemented for the maintenance of data security, including prevention of unauthorized access to, and amendment of, computer records. Hard copies of all computer records and computer disk copies of programs should, where possible, also be retained in order to overcome potential difficulties in comparing new data with data obtained using outdated/replaced software.

5.13.3 All technical data relating to the production of reference materials shall be retained in accordance with the requirements of 4.11.2.

5.14 Characterization

The reference material producer shall use and document technically valid procedures to characterize its reference materials. Where possible, the characterization should comply with the requirements of ISO Guide 35.

There are several technically valid approaches to characterizing a reference material as described in ISO Guide 35. These include carrying out measurements using:

a) a single primary (definitive) method, preferably in duplicate, by a single organization (which may consist of a number of separate laboratories);

b) two or more independent reference methods by one organization; the methods should have small measurement uncertainties relative to the intended use of the reference material; the characterization should be corroborated by additional methods or laboratories;

c) a network of qualified organizations using methods of demonstrable accuracy and having an assessment of known and acceptable measurement uncertainty;

d) a method-specific approach (interlaboratory study) giving only method-specific assessed property value(s).

Depending on the type of reference material, its intended use, the competence of the laboratories involved and the quality of methods employed, one approach may be chosen as appropriate.

The single primary (definitive) approach should only be carried out when the equipment and expertise enable it to ensure traceability to the SI system. More usually, a property value can be reliably assessed when its value is confirmed by several collaborators working independently and using more than one method, for each of which the accuracy, repeatability and reproducibility have been well established. Generally, the reference material producer should select collaborators in such a manner as to ensure meeting the objective of the production programme, including ensuring an adequate level of quality for the reference materials being produced, as defined by the producer and, where appropriate, the user.

5.15 Assignment of property values and their uncertainties

5.15.1 The reference material producer shall use documented procedures based on accepted statistical principles for the assignment of property values. These procedures should include, as appropriate:

a) details of the experimental designs and statistical techniques used;

b) policies on treatment and investigation of statistical outliers and/or the use of robust statistics;

c) whether separate, method-dependent property values are assigned when significant differences are established using different methods;

d) whether weighting techniques are used for contributions to assigned property values derived from different methods with different measurement uncertainties;

e) the methods used to assign measurement uncertainties to the property values;

f) any other significant factors which may affect the assignment of property values.

The reference material producer should never rely entirely on a statistical analysis of the characterization data when assessing the property values of interest. Outliers should not be excluded on purely statistical evidence until they have been thoroughly investigated and, where possible, the reasons for the discrepancies identified. Alternatively, the use of robust statistics may be appropriate in some cases.

When several methods have been used to characterize a reference material, difficulty may arise when the results show significant differences, in which case a property value based on the mean is inappropriate. It is essential in such cases that the reference material producer and its collaborators have considerable experience of the different methods and be able to give more or less weight to the results from the use of a particular measurement method. For example, the means from two (or more) measurement methods may differ statistically, but the results from both methods may agree within the measurement uncertainty of each method. In some cases, the results may be weighted according to the inverse of the variance of each method. In some cases, measurement methods will produce irreconcilable results and it may be necessary to assign separate property values according to the methods used (i.e. a method-specific approach).

In assigning uncertainties to the property values of interest, any uncertainties resulting from between-unit variations and/or from possible instabilities (both during storage and during transportation) shall be included.

In assigning the property values of interest, the reference material producer should consider establishing a group of independent experts whose responsibility is to check that all work, data and documents are fit for their purpose. It is also necessary for the reference material producer to demonstrate the traceability of the property values in accordance with the requirements of ISO Guide 35.

5.15.2 The reference material producer shall carry out an assessment of the uncertainties of the assigned property values.

This should always be based on a combination of the uncertainties arising from the corrections for recognized systematic errors, the uncertainties arising from possible systematic errors and the uncertainty due to random variations of repeated observations. Ideally, the latter should constitute the smaller proportion of the uncertainty of a particular property value. In some cases, it may be necessary to make uncertainty estimates based on experience with the measurement methods and their reliability. In such cases, the justification should be described.

The most important aspect of establishing the property values of the reference material being produced is an assessment of their measurement uncertainties. Every measurement has an uncertainty associated with it. Proper assessment and correction of all recognized and correctable systematic errors should be carried out and the uncertainties associated with these corrections assessed. An educated assessment of measurement uncertainty arising from possible systematic errors should also be made, for example, based on the results of intercomparisons.

5.16 Certificates and information for users

The reference material producer shall issue a statement or certificate, as appropriate, communicating information about the reference material; this shall include information on the property values, their meaning, their uncertainties at a defined confidence level and, where appropriate, the expiry date of the material. The statement or certificate shall also contain information for the user on the proper application of the reference material and on potential problems in its use. The contents of the certificates shall comply with the requirements of ISO Guide 31.

Annex A
(informative)

Examples of traceability of the property values of reference materials

A.1 Concept of traceability

The term traceability is increasingly used to describe the reliability of measurements, but it is not always clear what is meant. Essentially, traceability implies an unbroken path (with stated uncertainties) to some higher level of accuracy or authority. In an absolute sense, this means to the base system of measurement units [International System of Units (SI)] or their derivatives. However, it has been more generally defined in the International Vocabulary of Basic and General Terms in Metrology (VIM) as “the property of a result of a measurement whereby it can be related to appropriate standards, generally international or national standards, through an unbroken chain of comparison.” In other words, when the result of a measurement is described as traceable, it is essential to specify to what (values of) “appropriate standards” traceability has been established. It may be to a base unit of the SI (such as the ampere), to a mass fraction number, to a defined scale (such as pH or hardness) or to a value resulting from the use of a method described in a national or International Standard.

In the case of reference materials for physical properties, it is usually possible to establish traceability via a series of instrument calibrations to the appropriate base units of the SI. For example, the certification of a reference material for specific heat capacity is based on measurements of electrical energy, temperature and mass, all of which are readily traceable to the SI by means of instruments calibrated by or traceable to values obtained at national metrology laboratories.

In the case of reference materials for chemical composition, establishing traceability often involves more steps. For example, the analyte of interest is usually determined by the physical response of an analytical instrument only after carrying out a number of processes such as sampling, dissolution or extraction, as well as separation by chromatography or more traditional wet-chemical methods. Any or all of these processes may constitute links in the traceability chain, each with its own uncertainty. The analytical chemist must therefore assess how efficient each process has been in completely retaining the analyte, either unchanged or stoichiometrically converted to another chemical species up to the point that the traceability chain may be broken, and in separating it from substances which interfere with the final instrumental measurement.

When the property is expressed in terms of the *amount of substance*, the analyst is faced with a particular problem. Because of the extensive use of a balance in a chemical laboratory, the property values of most reference materials certified for chemical composition are expressed as mass fractions or mass/volume per mass (concentration), rather than amount of substance which must be expressed in moles/mass. However, working in mass is a very good approximation of working in moles. The reference material producer is therefore concerned with demonstrating that the methods used are the most reliable available for the determination of a particular analyte in a particular matrix and defining the units used, for example, grams of lead per gram of blood, or grams of DDT per gram of animal tissue.

A.2 Certification of reference materials

As noted in the main text, ISO Guide 35 recognizes four main procedures for the certification of reference materials:

a) measurement by a single, primary, definitive method in a single laboratory;

b) measurement by two or more independent reference methods in one laboratory;

c) measurement by a network of qualified laboratories using one or more methods of demonstrable accuracy;

d) a method-specific approach (interlaboratory study) giving only method-specific assessed property values.

A primary definitive method is considered to be one where the property "is either directly measured in terms of the base units of measurement or indirectly related to the base units through physical or chemical theory expressed in exact mathematical equations. The term can thus be used to include analytical chemical methods even where the result is not necessarily "in accordance with a definition of the unit" as required by VIM. Even where such a high quality chemical analytical method is available, it is desirable that two or more analysts make independent determinations, preferably with different experimental facilities.

Certification by interlaboratory testing presupposes the existence of a number of equally capable laboratories employing methods which have been independently validated, and implies that differences between individual results are statistical in nature and can therefore be treated by purely statistical procedures. Although this approach to certification is often unavoidable, it frequently provides only comparability between laboratories and can lead to apparent authority being given to wrong values, especially if the statistical treatment is allowed to predominate over chemical wisdom and judgement. A subset of this procedure is when the analysis is method-specific.

The traceability of reference materials can therefore range from a rigorous chain of instrumental calibrations back to the base units of the SI to the use of a well-defined reference method. In each case, the reference material producer needs to consider how to apply the relevant principle. What is essential, particularly for all certified reference materials, is that the certificate contain a statement of traceability indicating the principles and procedures on which the property values (together with their measurement uncertainties) are based. A numerical value without this additional information is generally considered unacceptable in a reference material certificate.

A.3 Practical examples

A.3.1 General

The problem of establishing traceability of certified values is considered in A.3.2 to A.3.7 for some of the main categories of chemical reference materials. It must be stressed, however, that if mass fractions of elements or compounds are certified, it is not sufficient to establish traceability for the determinand.

A.3.2 Gas mixtures

The certification of reference materials of this type is the most easily traceable of all materials for chemical composition in that comparisons (by gas chromatography or other analytical methods) can be made with primary mixtures prepared gravimetrically. The traceability of the primary standard is established by the traceability of the masses to national standards of mass, the atomic/molecular masses of the components, and by the purity of the components. It is also necessary to establish the stability of the mixture in gas cylinders at regular intervals and by comparing measurements on newly prepared mixtures with those which have been subjected to prolonged storage.

A.3.3 Metal alloys

There are probably more reference materials in this category than in any other, and most are certified by the procedure based on interlaboratory comparison using published methods. It is important, therefore, to note that the reliability of such methods has been thoroughly established. In the case of finely divided materials, the analysis usually involves dissolution of the alloy before application of the analytical procedure. Whilst not eliminating possible errors introduced by incomplete knowledge of the composition similar to a solution of the alloy samples under investigation, the analysis of synthetic solutions of a composition similar to a solution of the alloy of interest, prepared from "spectroscopically pure" metals, can provide valuable evidence for the validity of the analytical methods employed for certification.

A.3.4 Pure chemical compounds

It is usually not possible to determine the major constituent with sufficient accuracy to derive a meaningful value of purity, except for substances where accurate titrimetric methods can be employed. Methods based on the melting characteristics (e.g. differential scanning calorimetry) measure total impurity but require the substance to be stable at its melting temperature, and are only reliable when the system is ideal and the impurities do not form solid solutions in the main component. When direct methods are not applicable, the analytical chemist has therefore to seek to separate and determine all the individual impurities, including the water content, by as many techniques as possible. Chromatography is most useful for organic compounds because of the variety of separation and detection systems available, but the problem of failing to resolve impurities which are chemically very similar to the main component has always to be acknowledged.

The producer of a pure chemical should recognize that it is equally important to demonstrate the identity of the compound as well as its purity. The chemical literature is not free from compounds with wrongly reported structures, and evidence of identity should always be part of the traceability statement on a certificate of purity.

A.3.5 Trace elements in inorganic (including water) and organic matrices

The use of isotope-dilution mass spectrometry (IDMS) has overcome many of the problems associated with the determination of trace elements. Its capacity to compare number ratios of isotopic atoms of different masses without quantitative separation of the sample yields results which, in theory, are directly traceable to the mole. “Spiking” the sample with an isotope of the analyte element, followed by the creation of conditions under which isotopic homogenization can occur, enables the amount of substance ratios of analyte and spike to be determined by mass spectrometry and be largely free from matrix effects, which equally influence the analyte and spike.

A.3.6 Organic compounds in organic matrices and water

This category of reference materials probably presents the greatest problems in establishing measurement traceability. The category includes trace pollutants in organic matrices [e.g. polychlorinated biphenyls (PCBs) and dioxins in animal fat], trace pollutants in water (e.g. pesticides in public water supplies) and clinical chemical analyses (e.g. cholesterol in blood). Even IDMS may not be totally satisfactory, since it requires the availability of a spike of known purity which behaves in an exactly similar way to the analyte in the separation and extraction processes which follow its addition.

A.3.7 Compounds certified for other chemical properties

Some chemical properties cannot be expressed in the base units of the SI or their values are method-dependent. Nevertheless, traceability is equally important for such materials but it is traceability to a reference method.

For example, although conceptually pH has an absolute definition in physical terms, it can only be usefully attained by assigning values on a practical scale to one or more solutions of selected chemical compounds. Certification of property values for these solutions is based on electromotive force measurements of specified electrochemical cells under carefully defined conditions, and traceability of the property values of reference materials for pH is to this measurement procedure.

Many of the reference materials used in clinical chemistry are certified by the results of reference methods. The catalytic activity of an enzyme is evaluated by its ability to increase the rate of a particular chemical reaction under specified conditions of pH, temperature and concentration. The importance of using reference materials, rigorously traceable to a reference method, for the calibration of routine hospital instrumentation has only recently been recognized.

A.3.8 Materials certified for physical and engineering properties

The traceability of physical and engineering property reference materials ranges from actual physical representations of base or derived SI units (to transfer artifacts used to calibrate measurement systems or control manufacturing processes), to surrogates defined by convention or by international agreement and used to verify instrument performance. For a reference material such as the Josephson voltage array, traceability is unequivocal and transparent. The artifact is the realization of a basic quantum physics phenomenon; by definition, it represents

the Volt. In contrast, Rockwell C hardness test block reference materials, demonstrating linkage to SI units is another matter. The Rockwell hardness scale is an arbitrarily set scale for testing machines based on stated references that can and do change. Therefore, traceability has to be expressed in terms of machine performance criteria that have been developed experimentally and accepted by national or international consensus. The metrology supporting such reference materials is difficult to demonstrate but these, and similar types of reference materials, are necessary in order to provide traceability for a growing number of automated machine and robotically controlled measurement systems.

Like chemical composition reference materials, a number of physical and engineering property reference materials (for pH, particle size, X-ray diffraction, etc.) are consumed with use and so are characterized in batches and contained in appropriate commercially available packaging. But there are other reference materials where the designs of the primary containments are almost as important as the artifacts themselves. In the optoelectronics area for example, the aluminium metal housing of an optical fibre diameter reference material or the thermal barrier for the gallium arsenide substrate of coplanar waveguide artifact have been designed to: optimize measurement of the certified parameter(s) of interest, be attached to specific types of instrumentation only, be able to function properly and be rugged enough to give consistently reproducible results over long periods of time, and be well protected when not in use. These requirements are applicable to all certified reference materials but they take on an added sophistication when the reference materials being developed are for high-tech applications.

It must also be noted that many physical and engineering property reference materials are individually certified or calibrated and their periods of validity stated in the certificates. This information complies with ISO Guide 31 instructions, but for reference materials that are not consumed with use, it may not be sufficient. Some reference materials can be used time after time, and traditionally their certifications were deemed to be valid indefinitely (all other requirements having been met). This was certainly true of the previous-generation stage micrometer reference materials for scanning electron microscopes. However, certificates now state finite validation periods in order to comply with current international quality system requirements. For a ‘re-usable’ reference material, it has therefore become necessary to supply additional information in the certificate that states either the artifact must be replaced or can be recalibrated when the validation period is exceeded. Should re-calibration be a viable option, the information provided should also explain where such services can be obtained (e.g. from the reference material producer and/or from accredited laboratories).

A.3.9 Reference materials for molecular biology applications

Work in the scientific field of molecular biology has dramatically increased in recent years. Once the exclusive area of researchers, it has progressed to the point that measurement procedures and processes commercially developed to aid in the characterization and prevention of diseases, to provide tools for law enforcement and forensics, and to control the manufacture of genetically engineered foods and medicines must be validated. Clearly many new reference materials are in demand, but the complexity of the task has only recently been fully appreciated. The chemistry of molecular and microbiological organic substances is complicated and the materials themselves are often difficult to characterize, handle, package, store and certify. Even with costly protective measures in place, the stability of these materials is always questionable because changes are constantly occurring within the materials themselves; that is, the certified species are experiencing natural metamorphoses — even when kept under rigorously controlled conditions. Inexorable change is not an attractive feature in any certified reference material, but it can and must be managed in these types of materials. With the help of biologists and biophysicists, valuable insight can be obtained regarding the magnitude and predictability of the changes occurring. For example, the DNA profiling reference materials currently available to the law enforcement community do experience changes and therefore must undergo continuous retesting. However, by understanding the biology of the cell components that are most sensitive to change, manageable retesting schedules have been in place for several years. Experience with DNA profiling reference materials proves that molecular and microbiological reference materials are indeed viable. For the near term, however, the work will probably remain confined to a few national metrology institutes and even fewer commercial enterprises that have the array of technical and financial resources required to certify these reference materials.

Bibliography

[1] ISO 3534-1:1993, *Statistics — Vocabulary and symbols — Part 1: Probability and general statistical terms.*

[2] ISO 3534-2:1993, *Statistics — Vocabulary and symbols — Part 2: Statistical quality control.*

[3] ISO Guide 32:1997, *Calibration in analytical chemistry and use of certified reference materials.*

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

[5] ISO 9000 compendium:1998, *International Standards for quality management.*

[6] EN 45000 series:1989, *General criteria for the operation of testing laboratories.*

[7] GUM:1995, *Guide to the expression of uncertainty in measurement* (issued by ISO, IEC, BIPM, IFCC, IUPAC, IUPAP and OIML).

[8] *Accreditation for chemical laboratories — Guidance for the interpretation of the EN 45000 series of standards and ISO Guide 25*, Eurachem Guidance Document No. 1/WELAC Guidance Document WGD2, 1st edn., April 1993.