NABL 191

National Accreditation Board for Testing and Calibration Laboratories (NABL)

Specific Criteria for Reference Material Producer Accreditation

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1. INTRODUCTION

Reference Material Producer (RMP) accreditation activities are administered under the direction of the National Accreditation Board for Testing and Calibration Laboratories (NABL), involving Assessment Team and Accreditation Committee as recommending bodies. The Reference Material Producers are required to comply with all the requirements listed in the international standard ISO 17034: 2016 'General Requirements for the competence of Reference Material Producer', APAC TEC 1 – 008 'APAC Guidance on Reference Material Use and Production', ILAC P9 'ILAC Policy for Participation in Proficiency Testing Activities' and ILAC P10 'ILAC Policy on Traceability of Measurement Results'.

Requirements specified in ILAC P9:06/2014 and ILAC P10:01/2013 have been reproduced in respective NABL documents i.e. NABL163 'Policy for Participation in Proficiency Testing Activities' & NABL142 'Policy on Traceability of Measurements'. The Specific Criteria document i.e. NABL 191 must be used in conjunction with ISO 17034: 2016. It provides an interpretation of the later document and describes specific requirements for those clauses of ISO 17034: 2016 which are general in nature. Further, the RMP shall follow the national, regional and local laws and regulations as applicable.

2. SCOPE OF ACCREDITATION FOR A REFERENCE MATERIAL PRODUCER

NABL shall provide a scope of accreditation that describes the specific types of Reference Material (RM) that the RMP is competent to produce. Although RMP accreditation conveys competence as a producer (not as a laboratory), testing and/or calibration are integral components of RM production.

It is also recognized that the property values and the associated uncertainties for certain RMs may vary between batches/lots of RMs although they are produced by the same accredited production procedures. These variations should however be within the accredited ranges and uncertainties in order for them to be considered for coverage under the scope of accreditation.

RM produced shall be fit for purpose or its intended use. The production of RMs involves some activities that are not normally considered the activities of a laboratory. The term "production" is defined under clause 7 of this document). When used in this document, it includes all necessary activities and tasks leading to a RM supplied to customers. Where an organization only provides services such as the provision of reference values to a Candidate RM, it shall not be considered as a RMP.

For some types of RMs as well as for certain property values, a RMP may only be competent to produce a particular range and within a certain uncertainty of the property value. The scope of accreditation for all CRMs with numerical property values, except for those with identity and ordinal property values shall include both range and the uncertainty of the assigned values. CRMs with identification value (such as species identification) or where the property value is an ordinal number (such as a colour fastness chart) do not require an uncertainty value to be stated in the scope of accreditation.

Reference material producers shall define their scope of activities in terms of the types of reference materials (including the sample matrices, if applicable), the properties to be certified and the ranges of Assigned value, uncertainty and best reference value capability (as relevant) of the reference materials they produce, and their involvement in activities like testing, calibration and measurements in relation to homogeneity, stability and characterization assessments and their use of subcontractors in these tasks.

An example of a typical RMP scope of accreditation is shown in **Annexure I**.

Best reference value capability is the capability of the RMP to produce lowest uncertainty for the concerned RM within the said range in the scope of accreditation.

Categories, sub-categories and sub–sub categories of reference materials are given below and this appendix can serve as good guidance to describe the specific types of RMs that a RMP is accredited to produce.

RMP Accreditation Procedure is shown in **Annexure II.**

CATEGORIES OF REFERENCE MATERIAL

CATEGORY A: CHEMICAL COMPOSITION

Reference materials, being either pure chemical compounds or representative sample matrices, either natural or with added analytes (e.g. animal fats spiked with pesticides for residues analysis), characterized for one or more chemical or physicochemical property values.

A1: METALS

A1.1 Ferrous

Steels
Carbon steels
Low alloy steels
High alloy steels
Cast steels
Speciality steels
Irons
White cast irons
Ductile irons
Gases in metals

A1.2 Nonferrous

Aluminium alloys
Copper base alloys
Lead base alloys
Tin base alloys
Brasses
Bearing alloys
Titanium base alloys
Zirconium base alloys
Gases in metals

A1.3 Special Alloys

A1.4 Refractory Metals and Alloys

A1.5 Rare Earth Metals

A1.6 High Purity Metals

Solid forms
Spectrochemical materials
Spectrochemical solutions

A2: INORGANIC REFERENCE MATERIALS

A2.1 Ores and Minerals

A2.2 Cements, Clays and Related Products

A2.3 Ceramics, Glasses and Refractory Oxides

Carbides
Glasses

A2.4 Agricultural Chemicals and Fertilizers

A2.5 Solid Fuels

Coal and coke
Mineral content
Major elements
Trace elements

A2.6 Pure Chemicals

Stoichiometry standards (primary standards, secondary standards, working standards)
Chromatography standards
Pharmaceutical materials
Cosmetic materials

A2.7 Stable Isotope Materials

A3: ORGANIC REFERENCE MATERIALS

A3.1 Pure Organic Compounds

Compounds for elemental analysis
Compounds for molecular weight
Chromatography standards
Illicit drugs and their metabolites - (See also A8 Forensic Reference Materials)
Illicit drugs
- Delta-9-THC and other cannabinoids
- Amphetamine
- Methylamphetamine
- 3,4-methylenedioxyamphetamine
- 3,4-methylenedioxy-methylamphetamine
- 3,4-methylenedioxyethylamphetamine
- Diacetylmorphine
- Morphine
- Cocaine
- Lysergic acid diethylamide and isomers

Therapeutic drugs
Veterinary drugs
Steroids
Pesticides, herbicides, acaricides, etc
Metabolites of any of the above
Priority pollutants
- PCBs, PAHs, etc

Fine chemicals
Pharmaceutical materials
Impurities in drugs & Pharmaceuticals
Ayush Products
Herbal extract / Phytochemical reference standards
Cosmetic materials
Isotopically labelled compounds

A3.2 Agricultural Materials, Fertilizers

A3.3 Foodstuffs

Proximate analysis
Nutritional properties
Vitamins
Other food additives
  Antioxidants
  Emulsifiers
Toxins
  Animal origin
  Plant origin
  Other biological origin
Trace elements
Trace organics
  Pesticide residues
  Antibiotic residues
  Other organic contaminants

A3.4 Plastics and Rubbers

Hardness
Natural rubber content
Identity
  Copolymers
  Plasticisers
  Vulcanising agents
  Blowing agents
  Antioxidants
  Fillers

A3.5 Petroleum Products

Fuels and lubricants
  Metals (Lead, Vanadium, Nickel etc)
  Non-Metals
  Physical Properties
  Chemical Properties
Transformer oils
  Moisture
  PCBs
Heat exchange fluids
  Moisture
  PCBs

A3.6 Vegetable Oils and Fats

Fatty acid profile
Triglyceride composition

A4: ENVIRONMENTAL REFERENCE MATERIALS

A4.1 Soils and Sludges

Trace elements
Mineral content
Trace organics
TCLP leachate

A4.2 Ashes

Fly ash from coal and coke
Incinerator ash

A4.3 Waters

Potable water
- Routine analytes
- Trace elements
- Organic pollutants
- Other analytes

Fresh water
- Major elements
- Trace elements
- Other analytes

Sea water
- Major elements
- Trace elements
- Other analytes

Industrial waste water
- Routine analytes
- Trace elements
- Organic pollutants
- Other analytes

Treated sewage
- Routine analytes

A4.4 Plant Material

Trace elements
Mineral content

A4.5 Marine

Fish - trace elements
Molluscs - mineral content
Plankton - organics

A4.6 BOD Reference Compounds

A4.7 Miscellaneous Biological Materials (e.g. Human hair)

A5: HEALTH AND INDUSTRIAL HYGIENE

A5.1 Clinical Laboratory Materials

A5.2 Ethanol Solutions

A5.3 Toxic Substances in Urine

Toxic metals
Fluoride
Mercury

A5.4 Drugs of Abuse in Urine

A5.5 Drugs of Abuse in Hair

A5.6 Materials on Filter Media

A5.7 Trace Elements in Blank Filters

A5.8 Lead in Paint (Powder and Sheet forms)

A5.9 Respirable Silica

A6: ENGINE WEAR MATERIALS

A6.1 Metallo-Organic Compounds

A6.2 Wear Metals in Oil

A7: Analysed Gases / Gas Reference Material

A7.1 Gas Mixtures (and High Purity Gases)

A7.2 Trace Volatile Organic Compounds

A8: FORENSIC REFERENCE MATERIALS

A8.1 Ethanol Reference Standards

Ethanol
Ethanol, aqueous solutions containing 0.050, 0.150, 0.250 g/100mL

A8.2 Drugs (individually named) and Metabolites*

In whole human blood and urine (*metabolites to include glucuronides).
See also A3.1 Pure Organic Compounds.

A8.3 Glasses

Bottle
Window
Automotive
Spectacle

A8.4 Paints

Automotive
Architectural

A8.5 Accelerants

Flammable liquids and residues thereof

A8.6 Explosives and Primers

A8.7 Gunshot Residues

A8.8 Noxious Substances

Crowd control agents
capsaicin
o-chlorobenzalmalononitrile (CS)
chloroacetophenone (CN)

A8.9 Examination Documents

A9: ION ACTIVITY
A9.1 pH Standards
A9.2 Ion Selective Electrode Calibrants
A9.3 Conductivity Standards
A9.4 Buffer Systems

CATEGORY B: BIOLOGICAL AND CLINICAL PROPERTIES

Materials similar to Category A, but characterised for one or more biochemical or clinical property values.

B1 GENERAL MEDICINE
B1.1 Human Serum Materials (powder and solution forms)

B2 CLINICAL CHEMISTRY
B2.1 Proteins
B2.2 Apolipoproteins
B2.3 Enzymes
B2.4 Hormones
B2.5 Trace Elements
Lead and cadmium
B2.6 Routine Blood Analytes like urea, uric acid, glucose etc.

B3 TISSUE PATHOLOGY AND CYTOLOGY

B4 HAEMATOLOGY
B4.1 Blood

B5 IMMUNOHAEMATOLOGY

B6 IMMUNOLOGY

B7 PARASITOLOGY

B8 BACTERIOLOGY AND MYCOLOGY
B8.1 Reference cultures
B8.2 Antibiotics

B9 VIROLOGY

B10 OTHER BIOLOGICAL AND CLINICAL REFERENCE MATERIALS

B11 FORENSIC REFERENCE MATERIALS
Purified DNA of known and continuing genetic composition
Human, primate and animal blood
Animal hairs
Fibres

CATEGORY C: PHYSICAL PROPERTIES

Materials characterised for one or more physical property values, e.g. melting point, viscosity, density.

C1 REFERENCE MATERIALS WITH OPTICAL PROPERTIES

C1.1 Optical Rotation

C1.2 Refractive Index

C1.3 Spectral Absorbance

Visible

Ultraviolet

Infrared

C1.4 Specular Reflectance

C1.5 Colour

White reference material (opal glass)

Ceramic tiles

C2 REFERENCE MATERIALS WITH ELECTRICAL AND MAGNETIC PROPERTIES

C2.1 Dielectric strength

C2.2 Resistivity

C2.3 Magnetic susceptibility

C3 REFERENCE MATERIALS FOR FREQUENCY MEASUREMENTS

C4 REFERENCE MATERIALS FOR RADIOACTIVITY

C4.1 Radiation Dosimetry

C4.2 Radiopharmaceuticals

C4.3 Labelled Compounds

C4.4 Natural Matrix Materials

C4.5 Carbon-14 Dating

C5 REFERENCE MATERIALS FOR THERMODYNAMIC PROPERTIES

C5.1 Calorimetry

C5.2 Thermal Conductivity

Metals

Pyrex glass

Resin-bonded fibre board

C5.3 Vapour Pressure

C5.4 Thermal Expansion

C5.5 Thermal Resistance

C5.6 ITS-90 Temperature Fixed Point

C5.7 Curie Point

C5.8 Boiling Point

C5.9 Melting Point

C5.10 Thermal Analysis Standards

C6 REFERENCE MATERIALS FOR PHYSICOCHEMICAL PROPERTIES

C6.1 Density

C6.2 Viscosity

C6.3 Surface Tension

C6.4 Molecular Weight

C7 REFERENCE MATERIALS FOR FIBRE IDENTIFICATION

C7.1 Natural Fibres

Animal hairs

Plant fibres

C7.2 Synthetic Fibres

Organic polymers

Inorganic fibres

C7.3 Asbestos Fibres

Crude fibres

Mounted specimens for fibre counting

C8 REFERENCE MATERIALS FOR OTHER PROPERTIES

C8.1 Shear Testing of Powders

C8.2 Minerals for X-ray Diffraction

CATEGORY D: ENGINEERING PROPERTIES

Materials characterised for one or more engineering property values (e.g. hardness, tensile strength, surface characteristics, etc).

D1 SURFACE FINISH

D1.1 Surface Roughness

D1.2 Corrosion

D1.3 Abrasive Wear

D1.4 Properties of Films and Surfaces

Nominal thickness

- X-Ray fluorescence
- Beta particle backscattering
- Ion beam sputtering

D2 SIZING

D2.1 Particle Size

Particulate materials

Latex sphere suspensions

D2.2 Surface Area

D3 NON DESTRUCTIVE TESTING

D3.1 Dye Penetrant Test Blocks

D3.2 Artificial Flaw for Eddy Current

D3.3 Magnetic Particle Inspection

D4 HARDNESS

D4.1 Hardness Standardised Block (Rockwell/ Vickers/ Brinell)

D4.2 Microhardness

D5 IMPACT TOUGHNESS

D5.1 Charpy Impact Standardised Blocks (Notches U/V/ Keyhole)

D5.2 Izod Impact Standardised Block

D6 TENSILE STRENGTH

D7 ELASTICITY

D8 CREEP

D9 FIRE RESEARCH

D9.1 Surface Flammability

D9.2 Smoke Density

CATEGORY E: MISCELLANEOUS

E1: OTHERS

3. TERMS & DEFINITIONS (Key definitions from ISO Guide 30: 2015 (E) & ISO 17034: 2016)

Reference material (RM)

Material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process

Note 1 to entry: RM is a generic term.

Note 2 to entry: Properties can be quantitative or qualitative, e.g. identity of substances or species.

Note 3 to entry: Uses may include the calibration of a measurement system, assessment of a measurement procedure, assigning values to other materials, and quality control.

Note 4 to entry: ISO/IEC Guide 99:2007 has an analogous definition (5.13), but restricts the term "measurement" to apply to quantitative values. However, Note 3 of ISO/IEC Guide 99:2007, 5.13 (VIM), specifically includes qualitative properties, called "nominal properties".

Certified reference material (CRM)

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

Note 1 to entry: The concept of value includes a nominal property or a qualitative attribute such as identity or sequence. Uncertainties for such attributes may be expressed as probabilities or levels of confidence

Note 2 to entry: Metrologically valid procedures for the production and certification of RMs are given in, among others, ISO Guides 35.

Note 3 to entry: ISO Guide 31 gives guidance on the contents of RM certificates.

Note 4 to entry: ISO/IEC Guide 99:2007 has an analogous definition.

Candidate reference material

Material, intended to be produced as a reference material (RM)

Note 1 to entry: A candidate material has yet to be characterized and tested to ensure that it is fit for use in a measurement process. To become an RM, a candidate material needs to be investigated to determine if it is sufficiently homogeneous and stable with respect to one or more specified properties, and is fit for its intended use in the development of measurement and test methods that target those properties.

Note 2 to entry: A candidate reference material may be an RM for other properties, and a candidate reference material for the target property.

Matrix reference material

Reference material that is characteristic of a real sample EXAMPLE Soil, drinking water, metal alloys, blood.

Note 1 to entry: Matrix reference materials may be obtained directly from biological, environmental or industrial sources.

Note 2 to entry: Matrix reference materials may also be prepared by spiking the component(s) of interest into an existing material.

Note 3 to entry: A chemical substance dissolved in a pure solvent is not a matrix material.

Note 4 to entry: Matrix materials are intended to be used in conjunction with the analysis of real samples of the same or a similar matrix.

Commutability

Property of a reference material (RM), demonstrated by the equivalence of the mathematical relationships among the results of different measurement procedures for an RM and for representative samples of the type intended to be measured.

Note 1 to entry: See also ISO/IEC Guide 99:2007,[1] ISO 17511:2003.[7]

Reference material certificate

Document containing the essential information for the use of a CRM, confirming that the necessary procedures have been carried out to ensure the validity and metrological traceability of the stated property values

Note 1 to entry: The required and recommended content of a reference material certificate is described in ISO Guide 31.

Product information sheet

Document containing all the information that is essential for using an RM other than a CRM

Reference material producer

Body (organization or company, public or private) that is fully responsible for project planning and management; assignment of, and decision on property values and relevant uncertainties; authorization of property values; and issuance of a reference material certificate or other statements for the reference materials it produces

Subcontractor

Body (organization or company, public or private) that undertakes aspects of the processing, handling, homogeneity and stability assessment, characterization, storage or distribution of the reference material under its own management system on behalf of the reference material producer

Note 1 to entry: According to ISO 17034 key tasks/aspects of the RM production process, which cannot be performed by external parties are project planning, assignment and decision on property values and relevant uncertainties, authorization of property values and issuing of reference material certificates or other statements for the RMs.

Note 2 to entry: The concept "subcontractor" is equivalent to the concept "collaborator".

Note 3 to entry: Advisors, who could be asked for recommendations, but who are not involved in decision making or the execution of any aspects mentioned in the definition above, are not considered as subcontractors.

Impartiality

Presence of objectivity

Note 1 to entry: Objectivity means that conflicts of interest do not exist, or are resolved so as not to adversely influence the activities of the reference material producer.

Note 2 to entry: Other terms that are useful in conveying the element of impartiality include "independence", "freedom from conflict of interests", "freedom from bias", "lack of prejudice", "neutrality", "fairness", "open-mindedness", "even-handedness", "detachment", "balance".

[SOURCE: ISO/IEC 17021-1:2015, 3.2, modified — In Note 1 to entry, "certification body" has been replaced by "reference material producer".]

Operationally defined measurand

Measurand that is defined by reference to a documented and widely accepted measurement procedure to which only results obtained by the same procedure can be compared

Note 1 to entry: Examples include crude fibre in foods, impact toughness, enzyme activities and extractable lead in soils.

4. GENERAL REQUIREMENTS

4.1 Contractual Matters

When reviewing requests, tenders and contracts, RMPs shall ensure that the requested matrix, property values and their metrological traceability and measurement uncertainty meet the need of the customer. In some cases, the stability time required should also be included in the review. If necessary, the RMP should give advice to the customers and help them to determine their needs.

If the requirement is Market driven or through survey then formal contract agreement may not be needed for those cases. However, the RMP shall ensure its capability before starting up the activity.

Note 1: Capability means that the reference material producer has access to, for example, the necessary equipment, knowledge 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 capability can include an assessment of previous reference material productions and/or the organization of inter laboratory characterization programmes using samples of similar composition to the reference materials to be produced.

Note 2: A contract can be any written or verbal agreement.

Note 3: A request to prepare a specific RM can originate from the RMP itself.

4.2 Impartiality

RMP activities shall be undertaken impartially and structured so as to safeguard impartiality.

The organizational structure shall be such that there is no conflict of interest with other activities, defining the responsibilities: this may be seen where organization defines the structure particularly in case of In-house reference material producers or where the RMP is the part of larger organization. For being impartial, RMP shall conduct its activities without any bias. Results of the RMP activities should not be compromised due to being influenced by any relationships of the personnel involved in the activities of the RM producer, with its customer.

To safeguard the impartiality in an organization wherein there are other activities in addition to the RM production, RMP shall clearly define the segregation of the other activities in its organization which may be vulnerable to risks to impartiality.

Risks to impartiality may also arise within the RMP itself by means of creating undue pressure on the technicians to skip the procedural steps for faster production of batches or to overlook the adverse results

which will distress a customer. Further undue pressure may also include offering monetary incentives to the employees for faster production of RM material. It is suggested that the identification of risks to impartiality should be carried out on an on-going basis or at a regular interval.

Also, looking at the external risks to impartiality, there are following possibilities as given below which may cause the bias:

- Business relationships between the RMP and the customer;
- Family or personal relationships between persons of the RMP who are involved in production activities and the customer

It is worth mentioning that simply by having a relationship with a customer does not necessarily lead to a risk to impartiality, however, the RM Producer is required to identify the potential risk and thereafter demonstrate that the risk has been eliminated or mitigated.

4.3 Confidentiality

Legally enforceable commitments may be in the form of contract / agreement / work order between the RMP and its customer.

5. STRUCTURAL REQUIREMENTS

RMP shall provide one of the following documents in support of its legal status claimed:

Type of Legal Identity	Document(s) to be submitted
Proprietorship	Bank passbook/ Account statement and PAN of the laboratory
Limited Liability Partnership	Registration certificate under The Limited Liability Partnership Act, 2008
Company	Registration certificate under The Companies Act, 1956 or 2013
Societies/ Trust	Registration certificate under Societies Registration Act, 1860/ Registration under The Indian Trusts Act, 1882
Government	Gazette or Government Notification or self-Declaration on Letter head by Head of the organization

If the RMP is part of an organization which has laboratory/ inspection body, the roles of key personnel shall be clearly defined identifying any potential conflict of interest. In addition, the organization chart shall clearly define the position and relationship of RMP with other activities.

The designated personnel (howsoever named), responsible for implementation, maintenance and improvement of the management system of RMP should be familiar with and fully aware of the requirements of ISO 17034:2016, and principles applicable to the organization's field of accreditation / compliance. The competence shall be verified by NABL assessment team.

6. RESOURCE REQUIREMENTS

6.1 Personnel

Accredited / applicant RMP is required to select and appoint a person (however named) responsible for Quality management system, Technical management system and RMs approving officer. A person can perform more than one of these functions as long as he / she satisfies minimum requirements of qualification and experience subject to the conditions that the work load is adequately justified in relevance to scope and with deputies in each field in place.

The minimum qualification for the technical personnel shall be Graduate in Science/ Diploma in Engineering.

For a person to be approved as authorised signatory personal evaluation shall be done during assessment. The minimum qualification for the authorized signatory shall be Graduate in relevant field of science or Engineering & Technology with minimum 10 years experience (Out of which 5 years particularly in the manufacturing / testing of the material in the applied category).The relevant academic qualifications, experience and demonstration of technical competence to the assessment team shall be the basis for acceptance of authorised signatories.

Individuals who issue reference material / certified reference material certificate shall assume responsibility for the technical validity and accuracy of all information contained in the certificate. Those personnel shall have and demonstrate a sound knowledge of:

- ISO 17034:2016, Guide 30, Guide 31 & Guide 35, NABL Policy & Procedures and this document (NABL 191);
- the principles of the calibrations, measurements, analysis and/or tests they perform or supervise;
- the scope for which accreditation is sought;
- the facility's management system;
- sound understanding of quality control data including homogeneity / stability, characterization of property values, assignment of property value etc;
- knowledge of statistics, preparation of RM, etc
- measurement ranges and the estimation of the uncertainties of measurement associated with the test or calibration results for which the facility is accredited or seeking accreditation.

RMP official who releases results shall hold a position within the organisation which provides authority over the accredited activities and, where necessary, results to be rejected when they consider them to be inadequate.

RMP should have an official who is conversant with the subcontractor activities in order to verify the activities performed by subcontractors.

Where a RMP's approval process for assigning staff to critical tasks including the release of reference material results is found not to satisfy the requirements for accreditation, the RMP will be required to review all reports issued since the time non compliance to the standard requirement is determined and, if necessary, withdraw and/or issue replacement reports. The accreditation status of the RMP may also be reviewed.

6.2 Subcontracting

RMPs shall document, in the management system document howsoever named (e.g. quality manual) or related documents, their policy and procedures for sub-contracting.

A task which is originally performed by a competent subcontractor at the time of initial accreditation/assessment of competence cannot be subsequently carried out by the RMP itself unless its competence in that task has been demonstrated to NABL. For example, characterization of a RM by a single (primary) method may be carried out by a competent laboratory but may not be by the RMP itself if it does not have the expertise to enable it to ensure metrological traceability (see clause 7.12 of ISO 17034:2016). It may also be possible that the RMP may lack the necessary equipment for the tasks (e.g. homogenizer for homogenizing the candidate material, measuring equipment for characterization, etc.). In other words, if the characterization of a RM by a single (primary) method was initial carried out by a laboratory as per the RMP's system for subcontracting and the same was assessed as competent during initial assessment then this arrangement may not be suddenly changed without information to NABL. In all such cases a fresh assessment may be carried out by NABL for assessing competence as per the revised sub-contracting arrangement of the RMP.

NABL does not permit serial Sub-contracting (i.e. Subcontracting of Sub- contracted work).

There are some processes that are not allowed to be subcontracted. Such processes are:

1) Production planning,
2) Selection of Subcontractors
3) Assignment of Property Values & their uncertainties,
4) Authorization of property values & their uncertainties.
5) Authorization of RM documents

RMP may subcontract activities other than above to a competent subcontractor. However, the RMP shall ensure that such services are subcontracted to competent laboratories / agencies / organizations conforming to relevant requirements of ISO 17034:2016 and the relevant ISO standards as given below:

- A competent subcontractor is one which is accredited by an ILAC / IAF signatory accreditation body for the specific scope as per ISO/IEC 17025/ ISO 15189 for testing, calibration and measurement activities. RMP to ensure that subcontractor is complying with ILAC P9 for same or closely similar materials wherever available.

  Note: Assessor may decide the extent of specific scope in cases where accredited labs as per ISO/IEC 17025 or ISO 15189 are not available for specific equipment (e.g. NMR) / tests"
- For other activities like Material preparation, Material Handling and storage (including post certification testing) and Material Distribution & post distribution services, NABL accepts ISO 9001 Certification issued by certification bodies which are accredited by an IAF signatory accreditation body and whose certification scopes cover activities sub-contracted.

RMP shall cover the sub-contractor's activities in its internal audit schedule. (See clause 8.7 also). The Internal Audit of such subcontracted activities should preferably be carried out during actual execution of the job at the subcontractor site.

Subcontractor activities may also be assessed by NABL during RMP assessment.

Activities that can be subcontracted cover a part of the procedure for production including the following:

1) Processing
2) Homogeneity and stability testing
3) Characterization
4) Handling
5) Storage
6) Distribution

Primarily it is the responsibility of the RMP to demonstrate that the sub-contractor is competent to perform the concerned part of the procedure and the work is carried out and the results produced are of required quality. RMP shall also ensure that the subcontractor complies with all the relevant requirements as specified in clauses 6.1 (Personal), 7.2, 7.3 (Production planning and control), 6.4 (Facilities and environmental conditions), 7.4 (Material handling and storage), 7.5 (Material processing), 7.6 (Measurement procedures), 7.7 (Measuring equipment), 7.8 (Data integrity and evaluation), 7.9 (Metrological traceability), 7.10 (Assessment of homogeneity), 7.11 (Assessment of stability), 7.12 (Characterization).

The appropriate evidences, records, etc. shall be maintained and available with the RMP to demonstrate the above as well as the records of evaluation and re-evaluation of the sub-contractor as per defined frequency.

NABL shall invariably confirm the competence of sub-contractor through an assessment of the sub-contractor as relevant, however this does not absolve the RMP of its primary responsibility as stated above.

6.3 Provision of equipment, services and supplies

Same as per the standard ISO 17034:2016.

6.4 Facilities and environmental conditions

Suitability of the accommodation and environmental conditions for the production of a specific reference material should be assessed based on their effect on the quality and validity of the reference material being produced, including how they affect the:

a. Integrity of the reference materials;
b. Performance of laboratory equipment and compliance to the test/measurement methods and procedures;
c. Competent performance of laboratory staff;
d. Compliance with the conditions specified in the production plan.

Consideration of environmental effects on reference materials includes precautions necessary to prevent contamination and degradation (refer to 7.4.3 of ISO 17034:2016. The areas for the material preparation, preconditioning, testing or calibration and storage should be of adequate size, free from dust, fumes and other factors (such as excessive temperature, humidity and direct sunlight) which may affect the integrity of the reference materials. If the reference materials produced require refrigeration, refrigerators / freezers

of adequate capacity and capable of maintaining the required temperatures shall be available and temperature of these shall be monitored.

The potential effects of environment on equipment performance include corrosion, temperature, humidity, vibration, electrical power stability, dust, magnetic influence and electromagnetic influences. The operation of the equipment should be ensured such that the effect of such influences does not exist.

Accommodation and environmental conditions should also be assessed based on their effects on staff competence in performing specific activities. There should be sufficient space available for staff to perform their duties comfortably, with adequate provision of lighting and with precautions taken to minimize noise.

7. TECHNICAL AND PRODUCTION REQUIREMENTS

7.1 General requirements

The RMP shall address the requirements of this clause for the production of RMs, including CRMs.

- A CRM has at least one certified value
- 7.9 applies only to certified values
- 7.2 to 7.18 contain requirements for certified values and other property values where necessary.

7.2 Production planning

It is critical that, before the start of the production of reference material, a detailed production plan is available. It is understood that pilot studies may sometimes need to be carried out but the need of any pilot study should be considered at the planning stage. The production plan should be fully documented. There are requirements for each step of the production process given in ISO 17034:2016 and the RMP is required to provide evidence that, at the planning stage, these requirements are given full consideration, and if necessary, recommendations from advisory groups have been sought.

Note 1: Advisory group shall have the expertise to carry out the functions as required in clause 7.2.3 of ISO 17034:2016. Technical experts may be used on an ad-hoc basis either in-house or external (– eliminating conflict of interest). The terms of reference and membership criteria of the advisory group shall be documented. Records of the competence of advisory group shall be maintained. Also records of their participation in the planning process shall be maintained, if used.

The production plan may need to be reviewed regularly during the production process. If it is necessary to make any change to the plan, the effects of the change on the conformity with the requirements of ISO 17034:2016 should be evaluated. Changes should be approved by the person authorized (in accordance with clause 6.1.6 of ISO 17034:2016), to perform production planning of the reference material. Changes should be fully documented, and should include the reasons and justifications for the changes. If the changes can affect the contract with the customer, the customer should be consulted. Customer's agreement with the changes should be obtained and records maintained as required by clause 4.1.3 of ISO 17034:2016.

Production and purchasing of starting material largely depend on the type of CRM. Therefore, when planning to produce matrix CRM, starting material with suitable properties must be obtained in sufficient quantity. The starting material must be checked whether they are suitable for the production of the planned CRM.

When RM is produced in multiple batches, verification shall ensure the equivalence of the properties.

Typical format for Production planning document to include atleast the following information

S. No.	Title	Particular	Comments / Remarks
1.	Description of the RM (Including type, phase, usage / requirement		
2.	material selection / source of the material (including, where appropriate, sampling)		
3.	verification of the identity of the material		
4.	maintaining suitable environments for all aspects of production		
5.	material processing		
6.	choice of measurement procedures		
7.	validation of measurement procedures		
8.	verification and calibration of measuring equipment		
9.	specification of acceptance criteria for, and assessment of, homogeneity, including sampling		
10.	specification of acceptance criteria for, and assessment and monitoring of, stability, including sampling		
11.	designing and organizing appropriate characterization, including sampling		
12.	assessing commutability* (where appropriate)		
13.	assigning property values		
14.	establishing uncertainty budgets and estimating uncertainties of certified value(s)		
15.	defining acceptance criteria for measurand levels and their uncertainties		
16.	establishing metrological traceability of measurement result(s) and certified value(s)		
17.	issuing RM documents		
18.	ensuring adequate storage facilities and conditions		
19.	ensuring appropriate labelling and packaging of the RMs		
20.	ensuring appropriate transport arrangements		
21.	ensuring post-production stability monitoring, if applicable		
22.	Ensuring an adequate post-distribution service for RM Users		
23.	Details of Subcontractor used and for which activities		
24.	Advisory member		
25.	Batch Size of the Material to be produced		
26.	Secondary verification if any		

*Information on Commutability of Reference Materials is described in Annexure III.

7.3 Production Control

Although effective control of each stage of the production process is needed, there are also certain critical steps in each stage where the quality of the reference material can be significantly affected. An analysis of such critical control points can be carried out and a plan that is designed to ensure that these critical control points are effectively controlled and monitored is a useful means to ensure the quality of reference materials. If the activity for processing has been subcontracted, then RMP should establish the methodology of control over the subcontractor activity. Appropriate records for this purpose shall be maintained.

Records shall be maintained to provide evidence that there is effective control of each stage of reference material production, e.g. records of inspection, testing, etc.

7.4 Material Handling and Storage

It should be emphasized that the requirements of this section apply to all stages of the production - from the receipt of the raw material to the finished reference material. If during some stages of production, the material has to go out of the direct control of the RMP, the RMP should provide necessary written instructions to the party responsible for handling the material. When storing the material, the storage environmental conditions should be specified.

When the same equipment is used for different materials, the facility should ensure that no cross-contamination or carry-over contamination is taking place. Work instructions for cleaning of equipment, change over process, etc. shall be documented.

All persons handling the materials (including those of the subcontractor's (if relevant)) shall be trained on the proper handling procedures. They should be aware of the precautions to be taken whilst handling the material, as required by clause 6.1.3 of ISO 17034:2016. It is the responsibility of the RMP to ensure that the packaging and labelling of the reference materials meet the safety and transport related regulatory requirements.

Reference material must be stored separately from the test materials and other materials in such a way that any adverse effects on their quality/integrity as well as misuse and loss are excluded. If particular storage conditions are specified (e.g. cooling) compliance shall be monitored and documented. Where applicable, safety measures for occupational health and environmental protection are taken according to the relevant dangerous properties (toxic, flammable, explosive, radioactive etc).

Access to rooms and facilities where RM are stored as well as withdrawal of RM shall be regulated and documented.

7.5 Material Processing

Preparation of the material (such as drying, mixing of ingredients, spiking with analytes, etc.) is a form of material processing. The main purpose of further preparation of the starting material is to generate a homogeneous batch of stable material with property levels as required. In addition, the prepared material should be similar to the typical test samples used with the test methods for whose quality assurance the RM is intended.

The procedures for material processing, may include, as relevant, any of the activities as stated in clause 7.5.1 a) to i) of ISO 17034:2016.

These processes shall be included at the stage of production planning and documented work instructions shall be available and followed by the RMP or the Subcontractor, if sub-contractor is used for any of the activity.

Each of the material processing steps as described above may require to be subdivided in to different steps. In that case work instructions additional documentations shall be created. For example:

The packaging process generally includes following steps:

- Specification of packaging units and containers
- Splitting the batch among the packaging units
- Filling into the designated containers
- Labelling

When splitting the batch, homogeneity among the packaging units must be ensured.

The requirement of the containers depends on the type of reference material. General requirement are as follows:

- The container must be such that the reference material is protected against adverse effect of ambient condition (air moisture, oxygen, light etc.).
- The reference material must be inert against the inner surface of the containers.
- For storing the packaged material, appropriate storage conditions must be specified and appropriate storage capacity has to be made available. Storage conditions are derived from available information about stability relevant factors and where applicable dangerous properties of reference material according to the relevant regulations of dangerous goods.
- When the same equipment is used for processing different materials, the equipment should be thoroughly cleaned between uses to prevent possible cross-contamination.

All material processing procedures should be carried out by trained personnel and requirements of clause 6.1.3 of ISO 17034: 2016 are applicable.

When candidate reference materials are sent to subcontractors for testing, they shall be uniquely labelled, suitably packed and stored in suitable conditions during transport. Instructions on the storage conditions should be given to the subcontractors.

In cases where the certified values are based on data obtained in the material processing procedure, the requirements relating to the assignment of property values and their uncertainties apply to the material process procedures. In such cases, the material process procedures should comply with the requirements for measurement methods and metrological traceability given in clauses 7.6 and 7.9 of ISO 17034:2016. The requirements for measuring equipment given in clause 7.7 of ISO 17034:2016 also apply to those items of equipment used in the material processing stage which contributes to the uncertainty of the assigned values of the reference materials.

7.6 Measurement Procedures

Same as per the Standard ISO 17034: 2016

7.7 Measurement equipment

Same as per the Standard ISO 17034: 2016

7.8 Data integrity and evaluation

Homogeneity and stability assessments, characterization and assignment of property values and their uncertainties in all involve evaluation of data. The RMP shall use appropriate statistical techniques for data evaluation. The general and statistical principles for certification of a given reference material in ISO Guide 35, where appropriate, shall be followed.

7.9 Metrological traceability of certified values

The ILAC P 10 policy in regard to traceability provided by RMPs is:

1) The values assigned to CRMs produced by NMIs and included in the BIPM KCDB or produced by an accredited RMP under its accredited scope of accreditation to ISO 17034 are considered to have established valid traceability (see ILAC General Assembly resolution ILAC 8.12).
2) The values assigned to CRMs covered by entries in the JCTLM database are considered to have established valid traceability.
3) The majority of RMs and CRMs are produced by other RMPs. These can be considered as critical consumables and the laboratory shall demonstrate that each RM or CRM is suitable for its intended use as required by ISO/IEC 17025 or ISO 15189.

Metrological traceability is the property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.

Metrological traceability requires an established calibration hierarchy. For measurements with more than one input quantity in the measurement model, each of the input quantity values should itself be metrological traceable and the calibration hierarchy involved may form a branched structure or a network. The effort involved in establishing metrological traceability for each input quantity value should be commensurate with its relative contribution to the measurement result.

Metrological traceability of a measurement result does not ensure that the measurement uncertainty is adequate for a given purpose or that there is an absence of mistakes.

A comparison between two measurement standards may be viewed as a calibration if the comparison is used to check and, if necessary, correct the quantity value and measurement uncertainty attributed to one of the measurement standards.

The ILAC considers the elements for confirming metrological traceability to be an unbroken metrological traceability chain to an international measurement standard or a national measurement standard, a documented measurement uncertainty, a documented measurement procedure, accredited technical competence, metrological traceability to the SI, and calibration intervals (see ILAC-P10).

The suitability of the metrological traceability utilized by the RMP is important. In cases where the metrological traceability cannot be achieved through an unbroken chain of calibrations, clause 7.9 of ISO 17034:2016 provides other alternative means. If a CRM is used for establishing metrological traceability, the CRM used shall have comparatively small uncertainty (refer to Note below) and higher in the metrological traceability hierarchy. The uncertainties in the certified values of the CRM used shall be suitable for establishing metrological traceability appropriate to the RMs being produced.

Note: The RMP should consider the competence of the producer of any certified reference material it uses to provide the metrological traceability of the assigned value of its CRM. A competent RMP or testing/calibration organization which may be a National Metrology Institute which is a signatory to the CIPM MRA, participates regularly in BIPM or Regional Key Comparisons, and has the relevant CMCs been included in Appendix C of the BIPM Key Comparison Database (KCDB).

An illustration on Metrological traceability with example is given in Annexure IV.

7.10 Assessment of homogeneity

For a CRM it must be ensured that the certified values are valid for all packaging units. In addition, the certified values must be valid for all samples from a packaging unit. Under normal circumstances, the

degree of homogeneity assessment of a RM with respect to the property of interest should be performed. It is not acceptable to assume the homogeneity of a property value based on the assessment of another value unless correlation is demonstrated with analytes that are tested for homogeneity. If homogeneity testing is done only on a subset of the assigned values, the requirement given in clause 7.10.2 of ISO 17034:2016 applies.

When data from assessment of homogeneity are used for assigning the property values, the requirements for metrological traceability (Clause 7.9 of ISO 17034:2016) and characterizations (Clause 7.12 of ISO 17034:2016) apply to the test procedures used.

Note: Assessment of Homogeneity need to be done by RMP; however other related activities like testing, etc. as per initial planning may be sub-contracted.

7.11 Assessment and monitoring of stability

For a CRM it must be ensured that the certified values are valid until the end of utilization period (expiry date) specified in the certificate. This validity applies to unopened packaging units under proper storage. Under normal circumstances, stability assessment for each and every certified property value should be performed. It is not acceptable to assume the stability of a property value based on the assessment of another value unless correlation is demonstrated with analytes that are tested for stability.

Prediction of stability using a model is generally not acceptable unless such model is well established and widely accepted in the discipline concerned.

In cases where data from assessment of stability are used for assigning the property values, the requirements for metrological traceability (Clause 7.9 of ISO 17034:2016) and characterization (Clause 7.12 of ISO 17034:2016) apply to the test procedures used.

Stability assessment should include assessment of the effects of shipment. This includes studies with actual shipping under maximum stress conditions, e.g., distance, and temperature.

Stability assessment should include assessment of the effects of use. This includes studies with multiple subsamples and any requirements for changed temperature for storage before sub sampling. In stability testing the temporal change of certified values is investigated over an appropriate period. Any associated uncertainty could be expressed within the long-term stability assessment or as considerations described in the certificate.

Note: Assessment of Stability need to be done by RMP; however other related activities like testing, etc. as per initial planning may be sub-contracted.

7.12 Characterization

When a property value of interest is derived from an "empirical method", the RMP should use that particular "empirical method" for characterization. Details of the characterization procedures used should be recorded. When more than one laboratory is engaged for characterization, then all of them should use the same "empirical method". Such property values are only meaningful when applied to the same "empirical method". Therefore, to be more useful, the empirical methods used should be those published by standard writing bodies or widely recognized professional bodies in the field concerned**.**

An Extract from ISO Guide 35:2017 Cl 9 Characterization of the material is given in Annexure V

7.13 Assignment of property values and their uncertainties

As CRMs are often used by laboratories for establishing their metrological traceability, it is important that the uncertainties of the assigned values are estimated using methods which are generally more rigorous than for other purposes. The uncertainties include not just the measurement uncertainty of the characterization procedure but also other contributions.

Uncertainty in this Section covers both "measurement uncertainty" of a quantity value and "uncertainty" associated with a nominal property (i.e. property of a phenomenon, body, or substance, where the property has no magnitude e.g. colour chart, DNA sequence, etc).

The estimate of uncertainty should include at least the effects of characterization, homogeneity, transport and long-term storage. In case, the effects of any of the above are known to be zero then the same can be mentioned / recorded.

7.14 RM documents and labels

A reference Material document is a Document containing all the information that is essential for using any reference material. The reference material document covers both the product information sheet and reference material certificate.

This requirement pertains to the Certificates/documentation that is required to accompany the reference material as received by the user. A RMP may perform tests or calibrations for the production of reference materials. Such tests or calibration should be performed in accordance with relevant requirements of ISO/IEC 17025 or ISO 15189. It has to be however noted that the requirement for reporting of results

(such as clause 7.8 of ISO/IEC 17025:2017) only applies to internal testing and calibration reports and does not apply to certificates and documentation of the reference materials issued to users.

The contents of certificates for certified reference materials shall comply with the requirements of ISO 17034:2016 and ISO Guide 31. If the certificate also contains non-certified values, a clear distinction shall be made between certified and non-certified values.

The main intended use of an RM shall be stated. When the properties provided are independent of a particular analytical or measurement procedure, this statement is not intended to restrict the use for other purposes. The RM document shall provide sufficient information to the users so that they are able to decide whether or not the respective RM meets their requirements (e.g. matrix type, measurand, quantity level, etc.). Because there may be uses for which the material is not appropriate, or has not been sufficiently characterized, the RM document may include a statement explaining restrictions.

Examples of intended use of an RM other than a CRM are:

- to demonstrate control of a measurement process within a laboratory over a period of time;
- to check instrument performance;
- repeatability and reproducibility studies – repeated use over an extended period of time, instruments, operators, etc., to estimate long-term reproducibility or robustness of a measurement process or laboratory;
- to confirm the degree of equivalence of measurement results from two or more laboratories (e.g. provider and user), where the materials are inherently stable;
- to check operator variability;
- to investigate the impact of any changes to the environmental conditions (e.g. temperature, humidity).

Examples of intended uses for a CRM are:

- the realization of a fixed point of an (international) measurement scale;
- the calibration of instruments or measurement systems;
- the transfer of property values among different materials;
- the validation of analytical methods, in particular regarding trueness;
- the determination of the recovery factor of matrix separation operations such as extraction.

Instructions for the handling and use of the RM shall be stated. Examples of instructions for handling and use of an RM are:

- appropriate instructions to ensure homogenization of the container contents before use;
- prescribed instructions for the opening of the container;

- the exact conditions for the drying of the material and/or the dry mass correction;
- where necessary, instructions for further particle size reduction;
- appropriate instructions for the reconstitution of a solid RM to prepare a solution;
- appropriate mathematical expression for the calculation of the value of the property at the time of use, e.g. in the case of materials which are inherently unstable, such as radioactive substances.

The RM producer may include indicative values. Examples are:

- the approximate concentration of an analyte in a complex matrix that does not fulfil the criteria for a certified property value;
- individual results from each laboratory or analyst, where results from several laboratories or analysts were used to assign the property value(s).

It is advisable that neither (certified) property values nor indicative values are included on the label to prevent the use of the material without the information in the RM document having been studied.

The documentation for non-certified reference materials shall include information on homogeneity and stability and on the period of validity of the stated information. It shall also contain information for the user on the proper application and storage conditions of the reference material.

In some cases which are covered by specific legislation (e.g. most pharmacopoeia assay standards), the uncertainties of the assigned values are not stated since they are considered to be negligible in relation to the defined limits of the method-specific assays for which they are used.

The results of each calibration or measurement (or series of either) carried out by the RMP or the sub-contractor shall be reported in accordance with ISO/IEC 17025 or ISO 15189 and shall carry NABL symbol.

Internal reports of the RMP should not be confused with a Reference Material certificate or product information sheet which is supplied with a reference material to the customer.

An RMP is allowed to contract out some of its tasks to competent subcontractors. It may not be necessary to indicate which parts of the production process have been subcontracted in the certificate of CRMs or the documentation for RMs.

Certificates or documentation for a certified reference material or non-certified reference material should contain a unique identification of its production process. This identification may take the form of a reference number, the name of the process or in other suitable information.

A summary of the requirements is given in Table 1.

Content	Product Information Sheet	RM Certificate
Title of the document	Mandatory	Mandatory
Unique identifier of the RM	Mandatory	Mandatory
Name of the RM	Mandatory	Mandatory
Name and contact details of the RM producer	Mandatory	Mandatory
Intended Use	Mandatory	Mandatory
Minimum Sample Size	Mandatory whenever applicable	Mandatory whenever applicable
Period of Validity	Mandatory	Mandatory
Commutability	Mandatory whenever applicable	Mandatory whenever applicable
Storage information	Mandatory	Mandatory
Instructions for handling and use	Mandatory	Mandatory
Page number and the total number of pages	Mandatory	Mandatory
Document version	Mandatory	Mandatory
Description of the material Recommended	Recommended	Mandatory
Property of interest, property value and associated uncertainty	Optional	Mandatory
Metrological traceability	Optional	Mandatory
Measurement methods for method dependent measurands	Recommended	Mandatory whenever applicable
Name and function of the RM producer's approving officer	Optional	Mandatory
Measurement methods for method-independent measurands	Recommended	Recommended
Health and safety information	Recommended	Recommended
Subcontractors	Optional	Optional
Indicative values	Optional	Optional
Legal notice	Optional	Optional
Reference to a certification report	Optional	Optional

7.15 Distribution Services

Same as per the Standard ISO 17034: 2016

7.16 Control of quality and technical records

Technical records shall, as applicable, include all original observations and raw data and provide a traceable link between the reference materials produced and the information on the certificates or documentation of the reference materials. This applies equally to electronic and paper record systems. If a RMP uses an Information Management System, the system should meet all the relevant requirements, including audit trail, data security, safety and integrity, etc. It should be fully validated and records of validation should be maintained. RMPs should keep back-up copies of electronic records within their retention period. They should also have a system to ensure that electronic records remain accessible within that period even though the hardware and software of their computer system are being updated from time to time.

The record system should allow for ready retrieval of original observations and data pertinent to any issued reports or certificates.

For each Reference material produced, the records system should retain and provide ready access to the following detailed information:

(i) The full description of the reference material;
(ii) The unique identification of the reference material;
(iii) The test or calibration method or procedure used in the production process;
(iv) Identification of equipment and reference materials used in the production process;
(v) All data relating to the preparation and manufacturing of the candidate materials;
(vi) Original observations during the test or calibration and calculations based on the observed data;
(vii) Data and the statistical calculations for homogeneity and stability studies;
(viii) Data used in the assignment of property values and their uncertainties, including those data which have been rejected and the reasons for rejection;
(ix) Identification of persons performing the work;
(x) An exact copy/ Photocopy & not second/ third Original of the issued documentation or certificate of the reference material produced.

Original observations should be recorded immediately preferably into bound notebooks, or onto properly designed proforma worksheets using indelible pen. Instrument printouts should be kept when they are available. Where data processing systems are used, records of raw data should be retained (unless data are automated and stored electronically).

Errors in calculations and incorrect transfer of data are major causes of incorrect results. Calculations and data transfers should be checked by another person, then initialed and dated by the reviewer except in the case when there is no other suitable person available for this purpose.

7.17 Management of Non -conforming Work

Common examples of non-conforming work include environmental conditions in the testing or calibration areas exceeded the specified limits, tests performed using instruments with overdue calibration, acceptance criteria of quality control not met, and unsatisfactory performance in proficiency testing schemes, etc. It is important that RMPs should not just correct the problem but shall initiate actions which include a determination of the significance of the non-conforming work and this should include an investigation of whether the non-conforming work is an isolated incident or is due to some underlying causes with a possibility of recurrence.

In the latter case, corrective actions, in addition to corrections, are also needed. It should be emphasized that all personnel of the RMP need to be familiar with the procedures for handling non-conforming work and/or reference materials. They should follow the documented procedures whenever non-conforming work and/or reference material is identified. Training on the procedures is essential to ensure that relevant staff understands the procedures.

Records of nonconforming work and/or reference materials should be maintained as part of the RMP's quality records (The records should include information on the nonconforming work and/or reference materials, actions taken, results of evaluation of the significance and extent of the nonconforming work, etc). Internal audit should include checking the effectiveness of implementation of this aspect.

7.18 Complaints

Same as per the Standard ISO 17034: 2016

8. MANAGEMENT SYSTEM REQUIREMENTS

8.1 Options

ISO 17034:2016 describes two options for fulfilling the management system requirements, Option A & Option B. Besides meeting the requirements of Clause 4 to clause 7 of ISO 17034:2016, the RMP shall also implement a management system according to Option A or B.

Option A

RMP shall address the requirements of clause 8.2 to 8.11 as a bare minimum.

Option B

If a RMP has established and maintains management system in accordance with the requirements of ISO 9001:2015, these may be referred against the requirements of clause 8.2 to 8.11 of ISO 17034:2016 in the RMP's quality management system. Compliance to these requirements shall be verified during on-site assessment by NABL.

Note: When RMP is part of a larger organization, separate Quality policy to be defined for an RMP as the organization Quality policy may not match with the requirements of RMP quality policy.

8.2 Quality Policy (Option A)

Same as per the Standard ISO 17034: 2016

When RMP is part of a larger organization, clarity on relation of RMP with top management is to be given.

8.3 General management system documentation (Option A)

The management system of an RMP need not be complex and its format will depend on a number of factors including the size of the RMP, number of staff members and the range, volume and complexity of the work it performs. In cases where a RMP is part of a larger organization, RMP activities may already be incorporated in a document covering the organization's total range of operations.

Clause 8.2.3 b) requires the RMP to conduct all testing and calibration in support of the production of reference materials in compliance with the requirements of ISO/IEC 17025 or ISO 15189 as applicable.

If the RMP performs testing and measurement that significantly affects the uncertainty of the assigned property value of a RM, the RMP shall participate in the proficiency testing programs as required in ILAC P9 for the tests and measurements it performs. If a laboratory acts as a subcontractor, the RMP shall require the laboratory to participate in proficiency testing programs, as required to meet ILAC P9 for the tests and calibrations it performs. When proficiency testing programs are not available, other means to demonstrate competence, e.g. use of measurement audits and check samples, shall be considered.

8.4 Control of management system documents (Option A)

RMP shall have a master list of internal documents as well as external documents identifying the current revision status of documents in the management system, shall be established and be readily available to preclude the use of invalid and/or obsolete documents.

RMP shall define the periodicity for review of documents but the periodicity of the review shall be at least once in a year or earlier as per the policy defined by RMP.

RMP shall retain the obsolete documents for 2 years or more as per policy defined by RMP.

If the reference material producer's document 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. Amendments shall be clearly marked, initialled and dated. A revised document shall be formally re-issued within 3 months.

8.5 Control of records (Option A)

Same as per the Standard ISO 17034: 2016

8.6 Management review (Option A)

In accordance with a predetermined schedule and procedure, the reference material producer's top management shall periodically (Minimum once a year and preferably after Internal audit (IA) and / or after closure of IA Non – Conformities) conduct a review of its management 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 points (a) to (k)

The inputs to a management review should generally include the analysis and summary on the above topics, as relevant, instead of just an agenda having the above items listed.

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.

The typical format of the Minutes of Meeting of MRM may be:

S. No.	Agenda points	discussion	Decision taken	Time scale	Responsibility

8.7 Internal audit

The RMP shall, periodically (minimum once in a year) 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 management system and the requirements of ISO 17034.

The internal audit programme shall address all elements of the standard ISO 17034 including the technical and production activities leading to the finished product (reference material) and Sub- contractor's activities.

The audit program should generally include horizontal audit and/or vertical audit or both, so that all the sections/ departments are audited for every aspect/ clause of the management system and ISO 17034 standard.

The audits shall be carried out by qualified* (relevant qualification) and trained** personnel. The auditor shall understand the technical requirements they are auditing and are trained as per standard ISO 17034 including auditing techniques/processes. Records in form of Certificate shall be established as evidence of the internal auditor training.

* Relevant qualification for a chemical testing activity means that the personnel should at least have done graduation with Chemistry as one of the subjects. The Qualification requirement may be relaxed, provided a technical expert with relevant qualification, accompanies the trained personnel for conduct of audit. However, in exceptional cases, inter-department personnel can also conduct the internal audit ensuring independency of their activity.

** NABL accepts trained personnel who have preferably undergone a 4 day or 5-day training course from reputed organization as per ISO/IEC 17025 and/or ISO 15189 and gained knowledge on ISO 17034 (either through self-study self-evaluation mode or internal training or external training of at least 8 hours accompanied with a certificate). However, the trained personnel shall demonstrate the competence regarding understanding of requirements of ISO 17034 to the assessment team.

Internal audit shall be independent of the activity which is being audited. Personnel shall not audit their own activities.

Internal audit may be done by Internal person or external person (used for purpose of internal audit) to establish the extent of conformity of the RMP to documented requirements and/ or standard ISO 17034.

8.8 Actions to address risks and opportunities (option A)

Same as per the Standard ISO 17034: 2016

8.9 Corrective actions (option A)

Same as per the Standard ISO 17034: 2016

8.10 Improvements

Same as per the Standard ISO 17034: 2016

8.11 Feedback from Customers

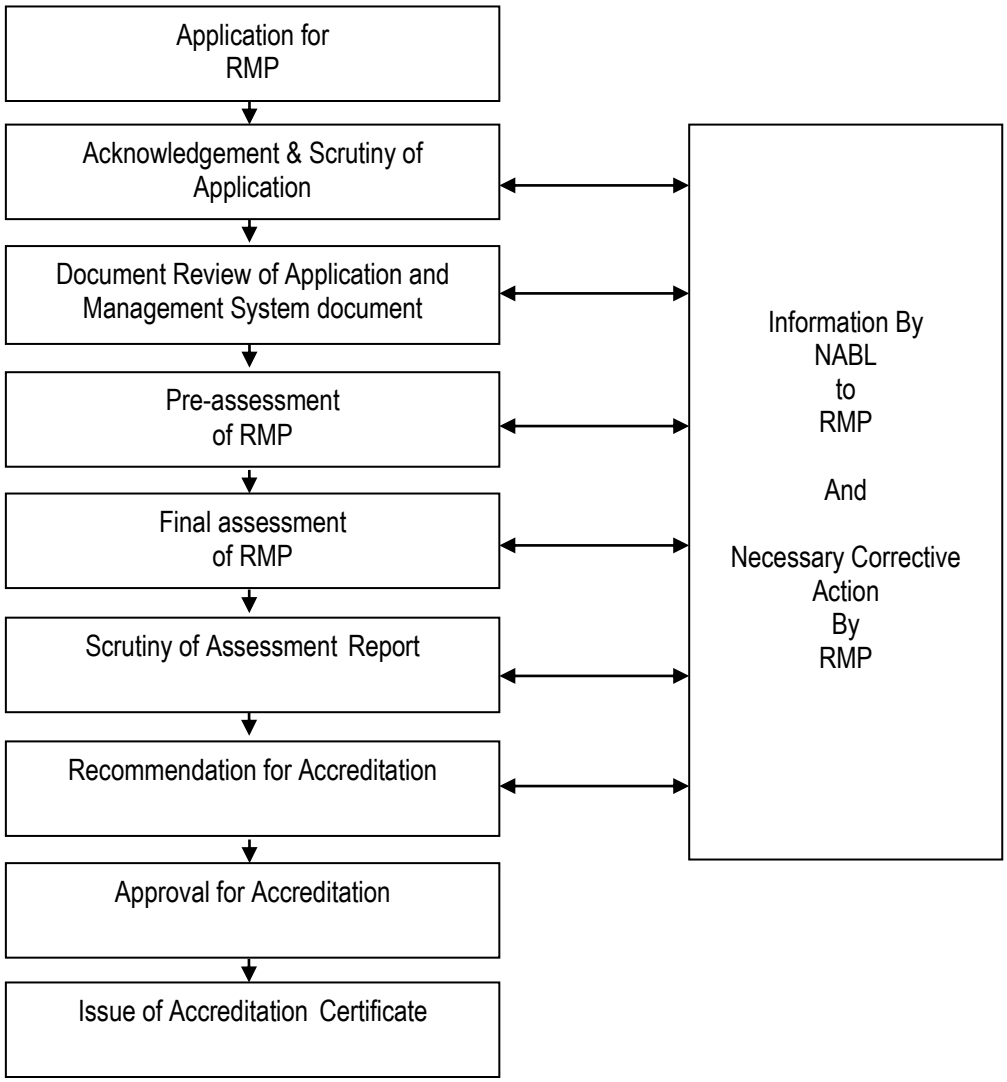
Same as per the Standard ISO 17034: 2016

ANNEXURE I

SAMPLE SCOPE

S. No	Types of reference materials (Certified Reference Materials, Reference Materials or both) Category & Subcategory	Reference Material Matrix or Artefact	Property / Properties Characterized	Range of property	Assigned value, uncertainty and best reference value capability (as relevant)	Approach used to assign property values/ Characterization Technique	Activities being subcontracted (e.g. assessment of homogeneity, stability, characterization, testing, calibration, measurements etc. if any)
1	Category: Chemical Composition Subcategory: Metals	Ferrous (Steels)	Carbon	0.08% - 1.10%	Assigned value-0.09% (MU-0.0001%) (Best reference value capability – 0.0001%)	Inter-laboratory comparison	Testing activity subcontracted to M/s ABC laboratory
2	Category: Biological and Clinical Properties Subcategory: Bacteriology & Mycology	Reference cultures	E. Coli	-	Qualitative	Primary method	Sub-contracting not done

ANNEXURE II
RMP Accreditation Procedure



ANNEXURE III
Commutability

Reference - ISO REMCO. Information on Commutability of Reference Materials (2014)

Reference material producers shall have a management system, procedures and service facilities that include the assessment of commutability "(where appropriate)".

The stated publication describes the typical circumstances in which commutability assessment by or on behalf of the reference material producer should, or should not, be considered necessary. In doing so the paper recognizes that the requirement differs considerably from one sector to another and in particular that commutability is of particular importance for clinical measurement.

In order to establish the necessity for commutability, and therefore of commutability assessment, it is necessary to consider the circumstances in which the reference material will be used, and in particular the characteristics of the relevant measurement procedures and the role of the reference material in the measurement process.

Characteristics of measurement procedures

The response of most analytical instruments and test kits to the quantity of interest is influenced by the nature of the test sample matrix, by interfering compounds present in routine test materials and, particularly in the case of substances with biological functions, by the particular form of the molecular or (sometimes) biological species of interest. The great majority of analytical measurement procedures are therefore developed to reduce this influence to an acceptable level. This is usually achieved by one or more of the following strategies:

- isolation of the substance of interest from the test material matrix and from other potentially interfering species prior to the actual measurement process, for example by thorough extraction and clean-up or purification.
- on-line separation technologies, usually chromatographic, which isolate the species of interest in the measurement process. Examples include liquid chromatography with on- line detection methods of limited selectivity, or coupled to more selective technologies as for example in the case of LC-MS-MS.

- sample pre-treatment – for example, digestion or dissolution – reduces the test material to a simple and well understood form which permits calibration using simple solutions of a certified reference material (CRM).
- special calibration strategies, such as the method of standard additions, which may allow the use of a pure material as calibrant in a complex matrix.

Where these strategies have been shown to operate acceptably, commutability is rarely an issue.

These strategies are, however, not always applicable or sufficient. This is particularly common for biological measurement procedures which are, for example, sensitive to conformation, secondary structure, or complexation, or for which aggressive sample treatment is not suitable. In these cases, a key strategy for calibration or quality control is to ensure that the behaviour of the calibrator and the measured

samples are consistent between measurement procedures, so that results of one (reference) procedure can reliably be used to calibrate another (usually a transfer procedure or routine test method). This calibration strategy requires assurance of commutability.

Role of the reference material in the measurement procedure

The measurement procedure covers all activities needed to produce a measurement result for a given test sample. This includes extraction and separation steps and the actual measurement process, that is, the signal producing step. Reference materials may be used for calibration of the entire procedure (usually with a matrix CRM), to determine the recovery of extraction or separation steps (usually with a matrix CRM which is not used for calibration of the same procedure), to calibrate the final measurement step (e.g. with a pure substance CRM transformed into a calibration solution) or for quality control of either part of the procedure or the entire procedure.

Assessment of commutability

When should commutability be assessed?

Reference material producers should ensure that a reference material is suited for its intended use. For calibrators and quality control materials this usually includes verification that the raw material selection and processing procedures result in a material with the same behavior as routine samples in the relevant measurement procedures. The assessment of commutability is part of the demonstration that such a reference material is fit for the intended use.

In some cases, it may be trivial to conclude on commutability. In other cases, the assessment should include a dedicated study. Examples of cases for which commutability is relevant are well known in the field of laboratory medicine; for example, solutions of glucose are not commutable for point of care blood testing devices. Commutability may also be relevant in other fields; for example, for Xray fluorescence measurements can be affected by the composition of the material and close matching of the matrix `composition between reference material and test sample is needed for accurate calibration.

Commutability assessment is always required when adherence to a particular documentary standard requires commutability assessment. For example, compliance with ISO 15194 will usually require commutability assessment.

For which methods and samples?

A commutability assessment, if required, should study:

- representative (typical and extreme) samples intended to be measured by a procedure (which may be a routine procedure or a “transfer” procedure designed to characterise secondary RMs) and the reference material(s) used to calibrate that procedure,
- the response of the reference material(s) and representative test materials to both the routine (or transfer) procedure and the reference method used to assign values to the reference material(s).

The relationship between these sets of responses gives an indication of the commutability of the material.

For which part of the measurement process?

Commutability of reference materials needs to be assessed for the part of the procedure in which the CRM is intended to be used.

If the reference material is only to be used for the calibration of the final measurement step, and not for the extraction, other separation or sample pre-treatment steps, then it is evident that the commutability of the reference material need only be assessed in comparison to the routine samples as they occur after the preliminary steps of the procedures to be assessed, i.e. at the start of the measurement step. It may not be necessary to assess the commutability, if there are good reasons to assume that the calibration solutions prepared from the reference material are behaving analytically equivalent with the samples measured.

In some circumstances, particularly in the case of immunoassay methods, the measurement step is not preceded by and separated from sample pre-treatments or extractions. This is the case if methods are capable of measuring directly in the matrix and are sufficiently robust to cope with matrix variations found in routine samples. In these circumstances the best available calibration strategy may be the use of a suitably matched calibration material containing a known amount of the species of interest, in the particular form to which the proposed routine measurement method responds.

Such matrix reference materials are usually different from routine samples in several aspects (e.g. storage, stabilizing agents). Therefore, the commutability of such matrix material should be assessed for the methods for which they are intended to be used.

Where the method for the property value assignment of the calibration material differs from the measurement method to be calibrated by the material, it is usually also important to establish that the signals from the proposed routine method and the signals from the value assignment method show at least a consistent (although not always linear) mathematical relationship under changes in the level of the species of interest. Also, here a commutability assessment is necessary prior to the use of the material for calibration.

Who should do the assessment?

Formally, the choice of calibration material and the verification that it is suitable for its purpose is the responsibility of the laboratory undertaking a particular measurement. However, where the reference material producer warrants that a reference material is appropriate for a particular intended use which requires a commutable material, the reference material producer is required to undertake an assessment of commutability. This requirement is, amongst others, laid down in ISO 15194.

Exceptions

There are circumstances in which commutability assessment is either unnecessary or impossible.

For example:

(i) For materials certified for a parameter that is fully structurally defined, for example, lead ions in water, it is trivial that the material is commutable for methods that indeed measure the analyte as defined.

(ii) It is not possible to assess commutability if only one method exists for the quantity intended to be measured. This is the case if the measurand is defined by an internationally recognised measurement procedure, or if at the current stage only one method exists.

(iii) A reference material produced for validation of a wide range of measurement methods may be intentionally poorly matched to provide an extreme challenge, allowing method developers to gain assurance of performance on extreme materials. Such a material should not be used as a calibrator, and commutability studies are not required.

(iv) Materials certified for purity do not normally require commutability assessment, though it may be important to show that the analyte is in a particular form (e.g. for proteins). However if calibration solutions are prepared from such a material the user should ascertain that the calibration solutions have the same analytical behaviour as routine sample within the analytical procedure. The evaluation of the commutability of such calibrators may be useful in this regard.

Commutability statement

Where commutability information is required the reference material producer must provide sufficient information for the end user to judge whether the material is appropriate for the specified use without further qualification, or whether additional qualification by the end user is required before use. In particular, the certificate or associated documentation must make clear;

- whether commutability studies• have been carried out,
- where a study has been carried out, for• which particular measurement methods or classes of measurement methods the material has been shown to be commutable and any for which the material has been shown not to be commutable,
- any differences between the reference• material and routine test materials which are known to the reference material producer and which might reasonably reduce commutability for other test methods (specifically: any differences in the levels of known metabolites of the species of interest; differences in form or structure of the species of interest; differences in preparation of the reference material, including the presence of stabilisers etc.; differences in accessibility of the species of interest, in particular whether the species of interest is within or outside cell membranes in the reference material and in routine test materials).

This information should be available to the end user prior to purchase.

Summary

1. It is appropriate, as required by ISO 15194, for a reference material producer to conduct an assessment of commutability where;

a. The intended use requires commutability of calibration or quality control materials and,

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

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

2. Where knowledge of commutability is important for the intended use, the producer should inform the purchaser of the material, via a statement on commutability, of any known factors related to commutability which materially affect the suitability of the material for calibration.

ANNEXURE IV
Metrological Traceability

Reference: Eurachem / CITAC Guide – Metrological Traceability in Chemical Measurement, 2nd Edition 2019

To achieve comparability of results over space and time, it is essential to link all the individual measurement results to some common, stable reference or measurement standard. Results can be compared through their relationship to that reference. This strategy of linking results to a reference is termed "metrological traceability."

Key elements in establishing traceability are as follows:

I. Specifying the measurand, scope of measurements and the target measurement uncertainty;
II. Choosing a suitable method of estimating the value, that is, a measurement procedure with associated calculation - an equation - and measurement conditions;
III. Demonstrating, through validation, that the calculation and measurement conditions include all the "influence quantities" that significantly affect the result, or the value assigned to a standard;
IV. Identifying the relative importance of each influence quantity;
V. Choosing and applying appropriate measurement standards;
VI. Estimating the uncertainty.

This list does not necessarily imply an order or priority among the activities; they are all important. Some interdependencies will also occasionally result in revisiting prior decisions. The important issue is that they are all carried out adequately for the purpose in hand. For consistency, however, the following paragraphs consider each in turn in the order above.

Note that these steps are sufficient for claiming traceability of results on the assumption that other QA measures, including staff training, measurement quality control etc. are in place.

An Example of Establishing Traceability

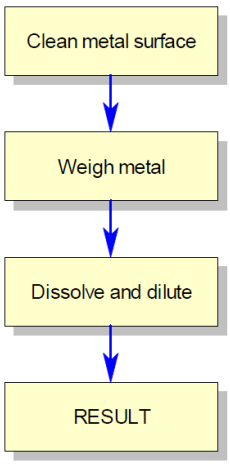
A1. Preparation of a calibration standard

Specify the measurand and the target measurement uncertainty

A calibration standard is to be prepared, for use within the laboratory, from a high purity metal 1000 mg l^{-1} with a required combined standard uncertainty≈(cadmium) with a concentration of 2 mg l^{-1} or smaller. The concentration is defined at 20 °C. Because of the small uncertainty required, the use of commercial calibration solutions is not feasible.

Establish the procedure to prepare the calibration standard

The surface of the high purity metal is cleaned to remove any metal-oxide contamination. Afterwards the metal is weighed and then dissolved in nitric acid in a volumetric flask.



The separate stages are:

I. The surface of the high purity metal is treated with an acid mixture to remove any metal oxide contamination. The cleaning method is provided by the manufacturer of the metal and needs to be carried out to obtain the purity quoted on the certificate.

II. The volumetric flask (100 ml) is weighed without and with the purified metal inside. The balance used has a resolution of 0.01 mg.

III. 1 ml of nitric acid (65% m/m) and 3 ml of ion-free water are added to the flask to dissolve the cadmium (approximately 100 mg, weighed accurately). Afterwards the flask is cooled and filled with ion-free water up to the mark and mixed by inverting the flask at least thirty times.

IV. The concentration is calculated from

$$c_{Cd} = \frac{1000 \cdot m \cdot p}{V} \qquad (\mathrm{mg}/\mathrm{l})$$

Where
c_{Cd} : concentration of the calibration standard (mg l^{-1})
1000 : conversion factor from (ml) to (l)
m : mass of the high purity metal (mg)
p : purity of the metal given as mass fraction (kg/kg)
V : volume of the liquid of the calibration standard (ml)

Mass, purity and volume are all part of the equation, and are consequently influence quantities and expected to be appropriately controlled. Noting that the specification of the measurand implicitly includes the temperature as a fixed value, it follows that the four values which need to be considered for traceability are mass, purity, volume and temperature.

Validation

Validation is a prerequisite in establishing traceability. For this simple and well-understood procedure, the principal influences are well known. However, an important assumption is the implicit assumption of complete dissolution of the material. To check this in practice, a simple cross-check against an independent preparation is normally sufficient. The validation therefore consists of two major parts. First a calibration solution with a similar combined standard uncertainty has to be obtained. This solution could be either the calibration solution used before in the same laboratory, a solution which has been prepared according to a different procedure, or a solution provided by a national standard program, like an SRM

solution from NIST. Second, the concentration of the two solutions has to be compared using an analytical technique with measurement capabilities sufficient to detect the kind of gross effect which might arise from incomplete dissolution or reprecipitation. On performing this check, using inductively coupled plasma optical emission spectrometry (ICP-OES), good agreement is found between observed and expected values. In the light of long experience of dissolution, this is sufficient to confirm the sufficiency of the simple specification.

Identifying the relative importance of each influence quantity

Mass, purity and volume are all clearly critical, since they form part of the calculation for the result. The relevant references will accordingly need to be chosen with close attention to their uncertainty. Temperature, however, is not part of the equation, it is useful to consider whether special attention is required. In 'worst case' check. The following effects (in mg l^{-1} Cd) of different temperature errors were estimated assuming aqueous solution:

Temperature error (°C)	Concentration error (mg l^{-1} Cd)
10.0	2.00
5.0	1.00
1.0	0.20
0.1	0.02

Clearly, the natural temperature range (represented by the 10 °C error is likely to be unacceptable. But an error of 5 °C leads to an error of only 1 mg l^{-1} Cd, significantly less than the required uncertainty. This is readily achievable in a routine laboratory with ordinary temperature control. It is likely that no additional measurement or calibration will be required, though temperature monitoring would be sensible.

Choosing and applying appropriate references

The mass *m* needs to be traceable to measurement standards with sufficiently small uncertainty. This is provided routinely by normal calibration procedures for the balance, and confirmed by the associated calibration certificate. Since calibration intervals are relatively long for analytical balances, the linearity is checked on a regular basis with the internal check weights of the balance to stay within the limits given in the manufacturer certificate. Its validity is further reviewed with daily check weights, which are traceable to national standards and capable of showing significant deviation from nominal values.

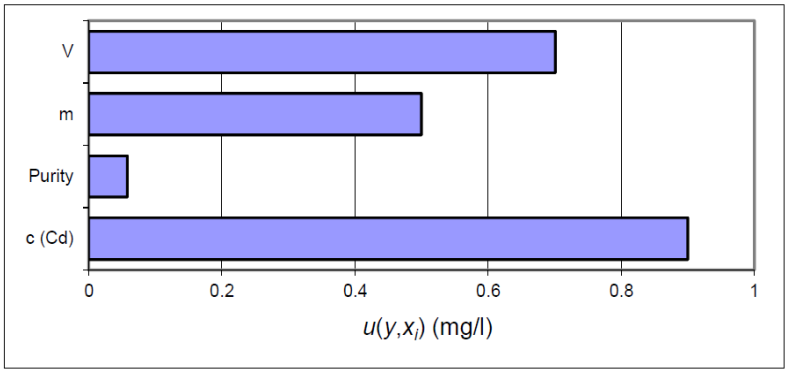
The purity is the certified property of a reference material, as certified by the supplier, and the uncertainty is demonstrably small enough for the purpose (see the uncertainty figures below). Provided that the metal surface is cleaned according to the instructions given by the supplier, purity can be considered traceable with adequate uncertainty.

The volume is measured using a flask chosen from a manufacturer who provides information about the traceability of the flask volume to a national standard, through a calibration certificate. The resulting uncertainty is a substantial contribution, but acceptable. Because glassware can deform slightly over time, and the glassware calibration is a dominant uncertainty source, the volume of the flask is checked regularly by weighing the given volume of water.

The flask has been calibrated with water at a temperature of 20 °C. A check on the laboratory temperature shows effective control within 20±4 °C, which is within acceptable limits as expected (see above), so equilibration of solutions at room temperature is sufficient. The laboratory temperature must clearly be monitored using a thermometer with a smaller uncertainty; in practice this can be readily achieved with an ordinary mercury-in-glass thermometer checked against a calibrated thermometer.

Evaluating the uncertainty

The overall uncertainty and major contributions are shown in the figure below. Note that the volume uncertainty includes a temperature uncertainty contribution equivalent to approximately 0.4 mg l^{-1}, based on an ambient temperature range of 20 ± 4 °C, confirming the acceptability of the ambient temperature control.



ANNEXURE V

An Extract from ISO Guide 35:2017 Cl 9 Characterization of the material
(In Few places text has been added for more clarity)

9 Characterization of the material

9.1 Preamble

The guidance in this clause is intended mainly for the measurements performed to assign the certified property values of a material (y_{char}). Studies for the determination of non-certified property values (however named), may also follow the principles outlined in this clause, but will in general require less rigour, especially with respect to evaluation of measurement uncertainties and establishment of metrological traceability (see 9.11).

It is important to note that a certified property value should be a good estimate of the true value and not just the average of a population. The certified value may be the same for many individual units (batch processing), or an individual value may be assigned to each unit in cases where a number of single artefacts are being produced.

For certified values, the associated uncertainty of characterization (u_{char}) should be determined. ISO 17034 requires an RM producer to provide evidence of the metrological traceability of the certified value to a stated reference. This means that whatever the approach chosen; the metrological traceability of the certified values should be clearly defined. Traceability can only be achieved if the values that are combined have been shown to provide valid estimates of the value of the measurand (as defined) within the claimed uncertainty and the results are traceable to the same metrological reference. Ideally, the International System of Units (SI) is the preferred metrological reference, but other references can be used. Metrological traceability also applies to operationally defined quantities; it remains essential to ensure traceability to defined metrological references by proper calibration.

Note 9.2 gives guidance on establishing metrological traceability for reference material characterization.

Characterization can be achieved by using one or several methods in one or several laboratories.ISO 17034 lists several basic approaches to characterization:

- using a single reference measurement procedure (as defined in ISO/IEC Guide 99) in a single laboratory;
- characterization of a non-operationally defined measurand using two or more methods of demonstrable accuracy in one or more competent laboratories;
- characterization of an operationally-defined measurand using a network of competent laboratories;
- value transfer from a reference material to a closely matched candidate reference material performed using a single measurement procedure performed by one laboratory;
- characterization based on mass or volume of ingredients used in the preparation of the reference material.

This clause provides guidance on these basic principles, as well as on the conduct of collaborative studies, characterization of purity and characterization by direct comparison with closely matched CRMs. While the current state-of-the-art is not sufficiently evolved to give detailed guidelines for the characterization of qualitative (nominal) properties (e.g. identity of the substance), some general principles are also listed in this clause.

9.2 Establishing Metrological Traceability

9.2.1 Principle

Metrological traceability is a characteristic of a measurement result. In practice, the traceability of a measurement result of a property value consists of two parts, namely the clearly defined identity of the measurand and the traceability of the property values of this measurand to the stated references

Note: The stated reference shall be a definition of a measurement unit through its practical realization, or a measurement procedure including the measurement unit, or a measurement standard. Where it is technically possible, the RMP shall demonstrate that the stated reference is traceable to the International System of Units (SI). The traceability to SI units is through National Metrology Institute(NMI) e.g. National Physical Laboratory (NPL), India. (Example - Through unbroken chain of comparison (higher order) to SI units).

Establishing traceability therefore includes both the proof of identity of the property measured and the comparison of the results to an appropriate stated reference. The comparison is established by ensuring that measurement procedures are properly validated, that measuring equipment is appropriately calibrated, and that any conditions of measurement (such as test material preparation, environmental conditions, etc.) are under sufficient control to provide a reliable result. An RM producer can ensure this in a number of ways, including validation of procedures and calibration of equipment under their control, or verification of traceability through the use of materials of known value. The following clauses give further guidance on these principles.

9.2.2 Metrological references

The traceability of measurement results is usually ensured through proper calibration of all relevant input quantities against appropriate measurement standards and/or certified reference materials. Quantity values can be traceable to

- a generally accepted system of units [e.g. the SI];
  (i.e. in simpler terms it is - quantity value can be traceable to SI units)
- measurement standards, including CRMs.

(i.e. in simpler terms it is - quantity value can be traceable to standards from NMI
e.g. Bhartiya Nirdeshak Dravya (BND xxxx) from NPL, India)

In most cases, laboratories will use measurement standards that carry values traceable to a higher reference (e.g. SI). This should be attempted wherever possible. Values obtained by calibration with such a standard are traceable to this higher reference via the standard, if all other input factors have been duly calibrated.

Note 1 Typical items to be calibrated include balances, thermometers, torque-wrenches, volumetric instruments, vernier calipers and stopwatches.

Note 2 In many cases, measurement standards, including CRMs, will be used as calibration standards for the measurement procedures. Examples are working standards (traceable to the primary standard) or conventional scales like pH, for which the agreed primary realization is the Harned cell and for which routine calibration uses buffer solutions. Values obtained by calibration with this standard are traceable to this higher reference via the values of the standard, if all other input factors have been properly calibrated.

Note 3 If the certified value of a CRM used for calibration is itself traceable to a higher reference (e.g. the SI), then the new CRM will be traceable to this higher reference via calibration with the CRM, if all other input factors have been properly calibrated.

Note 4 The relevance of input quantities is usually evaluated against the combined standard uncertainty of the measurement result. A common rule of thumb is to consider the uncertainty contribution of one input quantity relevant if it is larger than a third of the combined standard uncertainty

9.2.3 **Types of measurands**

A measured property can be

- defined without reference to a particular procedure for measurement. This is the case for basic physical properties (length, mass) and concentrations of clearly defined substances, which can be directly linked to the amount of substance (mole). In this case, the measurand is meaningful without reference to a particular measurement procedure.

- operationally defined. In this case, the measurand is defined by reference to a documented and widely accepted measurement procedure and only results obtained by the same procedure can be compared.

Whether or not the measurand is operationally defined, the establishment of traceability requires the same activity; every quantity that materially affects the measurement result should be subject to calibration or should be kept under suitable control, usually by use of calibrated instruments.

Example 1: The concentration of Cd in a sample is to be certified. The measurement procedures chosen are two validated procedures based on acid digestion followed by ICPMS and neutron activation analysis. The measurements are calibrated using certified solutions of cadmium. The results from two very different principles of measurement agree within their respective uncertainties. Together with the validation data and evidence of calibration, this provides confidence that bias for either procedure is small compared with the uncertainty showing that the measurand is not operationally defined and that the certified value is traceable to the stated reference.

Example 2: The mass fraction of crude fibre as defined by ISO 6865 is determined by an interlaboratory study in which all participants apply ISO 6865. All measurement conditions (temperatures, volumes, mass, etc.) were properly calibrated. The measurand is operationally defined (ISO 6865) and results are traceable to the SI.

Example 3: The mass fraction of crude fibre is determined by near-infrared spectrometry (NIR). The instrument is calibrated using measurement results obtained following ISO 6865. The measurand is

operationally defined (mass fraction of crude fibre as determined by NIR) and the quantity values are traceable to the results of ISO 6865.

Note: The results from the NIR procedure will usually have larger uncertainty than the defining procedure because the uncertainty must include the uncertainties of the calibration values as well as additional uncertainties arising from use of the NIR procedure, including allowance for possible procedure bias on the particular material.

9.2.4 **Effect of sample preparation or pre-treatment**

For many matrix reference materials, the situation is complex. Although the instrumental determination of the property value can be made traceable to appropriate units by the calibration of the measurement equipment used, pre-treatment steps such as extraction, pre-conditioning or transformation of the sample from one physical or chemical state to another cannot easily be calibrated. Such treatments can only be compared with a reference procedure (when available), or among themselves. This makes the clear definition of the measurand somewhat complicated. Generally, three possibilities exist:

a) For some treatments, reference measurement procedures have been defined and may be used in characterization studies to provide a certified value defined by reference to the reference measurement procedure. This gives an operationally defined quantity.

b) A second possibility is the use of two or more independent procedures to assess the procedure bias. If the results from independent procedures agree within their respective uncertainties, the RM producer may conclude that the values obtained are not significantly influenced by the individual procedures and hence the measurand is not operationally defined.

c) In other cases, only a comparison among different laboratories using the same procedure is possible. In this case, it is impossible to demonstrate absence of method bias; therefore, the result is an operationally defined measurand.

Example: The mass fraction of Cd in soil was determined in several laboratories that all used aqua regia extraction and subsequent quantification by ICPMS. The measurand is operationally defined as “obtained by aqua regia extraction and subsequent quantification by ICPMS”.

The definition of the property on the documentation provided to the users should reflect the characterization approach chosen.

9.2.5 **Verification of traceability**

In many cases, it is difficult to demonstrate the proper calibration of each and every piece of equipment. Such situations can arise because of unknown influence factors, but arise more frequently in characterization studies involving multiple laboratories, where obtaining calibration certificates for each and every instrument used is impractical. In these cases, the adequacy of the measures taken to ensure proper calibration of equipment and the traceability of results should be verified by, for example, specially designed and prepared control samples (such as a sample otherwise used for calibration) and CRMs. Agreement of results on quality control samples can be used as demonstration of sufficient calibration of all relevant input factors.

Note: Evidence of conformance with ISO/IEC 17025, including evidence from third party assessment, can be taken as additional evidence of traceability of the results reported by different measurement laboratories.

9.3 Characterization using a single reference measurement procedure (as defined in ISO/IEC Guide 99) in a single laboratory

9.3.1 Characterization by a reference measurement procedure without direct comparison with a CRM of the same kind

9.3.1.1 Concept

In this approach, a value is assigned by one laboratory using only one measurement procedure without direct comparison of a closely matched CRM. This limitation on the number of procedures and laboratories greatly limits the possibility to detect unexpected effects. Therefore, this approach requires the availability of a measurement procedure that is sufficiently well understood that unknown effects can be ruled out.

NOTE: "CRM of the same kind" refers to a CRM which matches the CRM to be characterized in all characteristics that might have an influence on the measurement result (matrix, measured property, quantity value of the measured property, etc.).

The results and their uncertainty are then used to determine the assigned value.

9.3.1.2 Measurement procedure requirements

Any measurement procedure used for this approach should fulfil the following requirements:

- it is completely understood, meaning that all steps have a sound theoretical foundation so that systematic error is negligible relative to the intended use;
- it is completely described by a measurement equation containing all relevant influence factors linking the measurand to the properties actually measured, all of which can be expressed in SI units;
- the measurement equation does not contain empirically determined factors that have a major influence on the measurement result (e.g. "recovery rates");
- there is no relevant influence of the measured quantity on any of the influence factors contained in the equation;
- the constants contained in the equation are known with a low uncertainty, which can be expressed in SI units;
- a realistic uncertainty budget can be written down in terms of SI units based on the individual quantification of the influence factors contained in the equation;
- the measurement uncertainty of the results obtained by the measurement procedure is sufficiently small for the intended use of the RM.

Establishment of the above requirements should be demonstrated by, for example, third party assessment, appropriate validation studies and measurement uncertainty evaluation in accordance with

ISO/IEC 17025, verification of performance by comparison with other laboratories, proficiency tests, and so on.

The assigned value is the result obtained by the reference measurement procedure. The standard uncertainty of the result is expressed as u_{char}.

In addition to measurements with the reference measurement procedure, it is highly recommended to perform confirmation measurements with an independent measurement procedure to confirm the absence of gross errors. While confirmation by an independent measurement procedure is not strictly necessary, it is nevertheless highly advisable to provide additional confidence in the results, even if the confirmatory measurement results have a higher uncertainty than those from the reference measurement procedure. The confirmatory procedure can also be used to demonstrate the applicability of the material to measurement procedures other than the reference measurement procedure used for characterization.

Results of potential confirmation measurements do not need to be combined with the results of the reference measurement procedure, as their uncertainty is generally much higher. Instead, the results from the different procedures are tested to determine whether the results of the independent procedure agree with those from the reference measurement procedure. If this is the case, there is no evidence of method bias. If this is not the case, the cause (either a bias in the confirmation procedure or an unexpected effect in the reference measurement procedure) should be identified and the result corrected, if necessary.

9.3.2 **Characterization by value transfer from a reference material to a closely matched candidate reference material using a single measurement procedure performed by one laboratory**

9.3.2.1 **Principle**

In this approach, values are assigned to a "secondary CRM" by directly comparing results on the candidate CRM with those on an already characterized and closely matched CRM (the "primary CRM"). Examples for such materials include trace element solutions measured against certified solutions, materials measured against Pharmacopoeia standards or absorbance standards measured against certified absorbance standards.

Note 1: Each measurement on a candidate CRM that requires calibration in fact compares it with another CRM (the calibrator). This clause deals entirely with the case where the two CRMs are so closely matched that a direct comparison in one laboratory using one method can be sufficient to assign a certified value. Using a CRM of a different kind (e.g. a pure solution for calibration of measurements on a matrix material) falls into one of the other characterization approaches.

For this approach, the secondary CRM should be sufficiently closely matched to make material-specific bias negligible, within the claimed uncertainty, from the primary CRM in all characteristics which have a significant influence on the measurement result. In this respect, the following aspects should be considered.

a) The primary and secondary CRMs consist of the same matrix. Small differences to allow for the establishment of calibration curves are acceptable, as long as the main characteristics of the material remain unchanged. The primary and secondary CRMs present the same analytical challenges for the method used.

Example 1: It is possible to characterize a solution of Cd in HNO3 against a certified solution of Cd in HNO3, as the matrix (diluted HNO3) of both CRMs is the same. It is not possible to characterize Cd in granite as a secondary CRM against a solution of Cd in HNO3 as the matrix differs. For many methods, the digestion step also adds an additional analytical challenge.

Example 2: If chromatograms of secondary CRMs show co-elution with the analyte of interest, it is impossible to characterize them as secondary CRMs. If the primary and secondary CRMs differ in complexity (e.g. multi-component secondary CRMs characterized against a series of unmixed single-component primary CRMs), the RM producer should demonstrate that this added complexity does not influence the result.

b) If the measurand is not operationally defined, the matrix is of a kind that, for the measurement in question, the measurement procedure can be regarded as completely understood.

Example 3: The chromatographic determination of a solution of benzo[a]pyrene is sufficiently understood, as no co-elutions or matrix effects occur. Determination of the benzo[a]pyrene in soil (or, in a soil extract) is not fully understood, as a multitude of factors can influence extraction efficiency and many co-elutions can occur.

c) The difference in the quantity level of the measured property does not result in a significant bias between the measurement results of the primary and secondary CRM.

Note 2: For chemical measurements, these conditions practically restrict the production of secondary CRMs to pure substances, solutions/dilutions of pure substances or operationally defined properties.

The measurement procedure used for characterization should fulfil all criteria for traceability listed in ISO 17034 and address the measurand for which the primary CRM is characterized.

The RMP should demonstrate the validity of the value and uncertainty transfer from the primary to the secondary CRM.

9.3.2.2 **Assigned value and u_{char}**

The assigned value is calculated by direct comparison between the results obtained on the primary and secondary CRMs. Valid methods include bracketing, multi-point calibration curves with the primary CRM, one-point calibration with a primary CRM of closely matched certified value and adding the measured difference to the certified value.

*u*char consists of a combination of the uncertainty of the certified value of the primary CRM, the uncertainty of calibration according to the chosen calibration model (which includes contribution due to the selectivity of the technique), and the effect of repeatability on the results of the secondary CRM. The calculated uncertainty should take account of the particular statistical treatment used to obtain the assigned value.

9.3.2.3 **Traceability**

The certified values of the secondary CRM are traceable, via the primary CRM, to the same reference as the values of the primary CRM.

Example: A solution of Cd in HNO_3 (secondary CRM) is characterized by measurement against a certified solution of Cd in HNO_3 (primary CRM). The certified values of the primary CRM are traceable to SI units. Therefore, the certified value of the secondary CRM is traceable to SI units as well.

9.3.3 **Selection of RM units for single-laboratory characterization**

The RM producer should use a measurement scheme (number of RM units, number of replicate results, etc.) that is capable of achieving the intended uncertainty for each certified value.

9.3.4 **Formulation methods**

This approach is usually applied for the production of calibration solutions from pure substances and also for gas mixtures, the production of which is described in a separate standard. The approach is sometimes also used in the production of matrix materials.

The value of the measurand and its uncertainties, in all materials to be mixed, has to be known in order to calculate a certified value and uncertainty. In many cases, this is equivalent to determining the purity of the material of interest (see 9.6) and confirmation of the absence of the material of interest in the material to which it is added (for example, a solvent or 'blank' matrix material).

It is important to guard against change in content between acquisition and mixing; for example, water loss or uptake should be excluded, where appropriate.

If gravimetric mixtures of several materials, all of which contain the measurand in question, are to be prepared, each of the materials should be characterized using one of the approaches described in this clause.

Volumetric production follows similar principles in the calculation of the assigned value and uncertainty but entails an additional need to pay close attention to non-additive volumes in mixing liquids (for example, ethanol/water mixture volumes are not the simple sum of the water and ethanol mixed) and other factors affecting measured volume, particularly temperature.

For the case of purely gravimetric production to certify a mass fraction, the assigned value y_{char} is calculated from the masses m_i of the individual components and the mass fractions w_i of each material as in Formula 12

$$y_{\text{char}} = \frac{\sum w_i \cdot m_i}{\sum m_i}$$

Formula 12

For the same procedure, the uncertainty u_{char} comprises all the uncertainties from the weighing steps as well as the uncertainties of the individual mass fractions. For the most common case of mixing two substances, this may be calculated from:

$$u_{\text{char}} = \sqrt{\left[\frac{m_1}{m_1+m_2}\right]^2 u_{w_1}^2 + \left[\frac{m_2(w_1-w_2)}{(m_1+m_2)^2}\right]^2 u_{m_1}^2 + \left[\frac{m_2}{m_1+m_2}\right]^2 u_{w_2}^2 + \left[\frac{m_1(w_2-w_1)}{(m_1+m_2)^2}\right]^2 u_{m_2}^2}$$

Formula 13

NOTE 1: Formula (13) does not include the covariance terms for correlated errors in weighing or the determination of w_i. Positive correlation effects can result in an increase in the combined uncertainty.

Although the result from the production is in principle sufficient for value assignment, it is highly advisable to check the result of the gravimetric production by measurement to detect any mistakes in the processing steps.

NOTE 2: A comprehensive discussion of the use of gravimetry in gas analysis is found in the literature (see, for example, References).

9.4 Characterization of a non-operationally defined measurand using two or more methods of demonstrable accuracy in one or more competent laboratories

9.4.1 Concept

9.4.1.1 **F**or many measurands, no reference measurement procedures are available that provide accurate results at the appropriate level of uncertainty. In these cases, it is necessary to find other means of improving the reliability of the assigned value. The approach described in this clause uses a number of data sets, obtained using different measurement procedures and/or in different laboratories to

a) demonstrate absence of significant bias in measurement procedures by showing that independent procedures yield the same results;
b) demonstrate the absence of significant laboratory bias for each laboratory by agreement among results;
c) improve the reliability of the assigned value by averaging results, thus reducing the effect of repeatability and randomizing and reducing the effect of between-laboratory or between-method variation.

9.4.1.2 The concept of the determination of the method-independent property values of an RM based on agreement among different measurement procedures, potentially performed in different laboratories, is based on at least two assumptions:

a) There exists a population of procedures and/or laboratories that is capable of determining the characteristics of the RM and providing results with acceptable accuracy.

b) For most data evaluation approaches, it is assumed that the differences between individual results, both within and between measurement procedures/laboratories, are random in nature regardless of the causes (for example, variation in measurement procedures, personnel or equipment).

9.4.1.3 For this approach to be valid, all results of all measurement procedures and/or laboratories involved should determine the same measurand and the results should be traceable (see 9.2.2) to the same system of units. This requires careful selection of calibration standards and careful investigation of the measurement procedures used. 9.4.2 describes selection of calibration standards.

NOTE 1: Even at the "state-of-the-art" level, differences in performance characteristics of measurement procedures as well as differences in the magnitude of uncertainty can exist between laboratories.

NOTE 2: There can be different objectives of interlaboratory comparisons, among them method validation, proficiency testing and characterization of reference materials. The goal of the study has important implications for the setup and evaluation of the various studies. It is therefore important to keep the goal of

characterization in mind and not to mix it with other purposes, even if it is logistically combined with, for example, a proficiency testing exercise (see A.3).

9.4.1.4 Inter-laboratory and multiple-method characterization rely in part on averaging across different sources of bias, to achieve a reduction in uncertainty. Effective averaging relies on representative sampling for different effects. This has important implications for the choice of participants and measurement procedures:

— Where possible, measurement procedures should be selected to give a good representation of different principles of measurement.

— The choice of participants should be representative of competent laboratories.

The choice of measurement procedures is discussed in A.1.1. The representative selection of participants is discussed in A.1.3.

9.4.2 **Study design**

At least two substantially different measurement principles should be included in a multiple-method study. For interlaboratory studies using many participants with free choice of measurement procedures, a good representation of measurement procedures suitable for the determination of the particular characteristic should be sought.

Consideration should be given to the choice of the calibration standard, i.e. whether each participant should use a standard of its choice or whether a common calibrant is provided to all participants. The purity of the calibrants used should be given due consideration.

Laboratories should be selected based on demonstrated competence. Therefore, participating laboratories should provide evidence of competence for the measurand in question independent of the measurements on the candidate CRM, ideally before commencement of the study. It is thus impossible to use data on the candidate CRM from the same study as demonstration of competence and for value assignment of a CRM (e.g. using the consensus value of results of a proficiency test study for value assignment of a CRM). (See also A.3.)

The RM producer should set a documented minimum number of technically valid results for which value assignment will be considered. The number of data sets should be large enough to provide a fit-for-purpose uncertainty in the estimated value after allowing for the possibility of failure to report, exclusion of results for technical reasons and the intended statistical evaluation.

NOTE 1: The number of participating laboratories is less important than the number of independent data sets. A single laboratory might be able to provide several data sets, all obtained by independent procedures, calibrants and/or instruments.

The organizer should implement adequate quality control measures to ascertain the quality of the results delivered.

The producer should specify the form of reporting. The specification should include

— instructions on reporting of individual observations, averages, or both;

— the measurement units required for quantitative results;

— the number of significant digits required for quantitative results;

— where appropriate, the form of measurement uncertainty required;

— the nature and form of additional information required by the RM producer (such as measurement procedures and measurement standards used, dates and times of measurement, or run order).

Reporting can consist of individual results for each replicate measurement with or without uncertainty or one single result with stated uncertainty, which leads to different approaches to review and evaluation (see Annex A).

The form of reporting may also include preformatted reporting forms for participants. The reports should contain sufficient detail to check the technical validity of results, including information on traceability.

Note 2: When reports are submitted in spreadsheet form, unintentional alteration can often be prevented by the use of 'locking' or 'protection' facilities incorporated in the spreadsheet software.

The organizer should provide sufficient guidance for participating laboratories and/or operators to ensure the smooth implementation of the work. To be successful, the interlaboratory study should have a well-defined objective, be effectively designed and be efficiently organized with clear, concise guidelines with which all involved can readily comply. Participation, either as operator or as laboratory, in such a programme implies agreement to adhere to these guidelines.

Note 3: Additional guidance on the organization of multiple-method studies in one or more laboratories is given in Annex A, which is an extension of this clause.

9.4.3 **Evaluation**

9.4.3.1 **Technical and statistical evaluation**

Data sets should be inspected visually and graphically. Data submitted by each laboratory should be checked for completeness and any observed anomaly should be examined carefully for possible trivial (transmission error, misprint, etc.) and non-trivial reasons (drop-out, equipment failure, etc.). If transcription errors are suspected, the laboratory in question should be contacted to query the reported values, but the expected value should not be given at this time. If errors or failures are confirmed, the corresponding results should be corrected or rejected.

All results should be checked for evidence of technical errors based on the information on the measurement procedures provided by the study participants. The technical evaluation should lead to a set of technically valid data, i.e. data that each taken alone would be regarded as an unbiased estimate of the true value.

Note 1: The term technical errors refer to measurement results that can be excluded from the data set based on scientific evidence. The term does not refer to measurement data that is shown to be outlying from the data set based solely on statistical considerations.

Note 2: Inclusion of quality control materials, with known values, in such studies has been found useful to identify technical problems.

The pool of technically accepted data sets should be evaluated statistically, giving due consideration to evidence of between group differences (particularly between-method and between-laboratory differences), the underlying distribution of values, presence of clusters of results and potential outliers. Appropriate statistical methods for the data set and property to be certified should be selected.

Where the producer requires reporting of measurement uncertainty, the technical and statistical review should also consider the validity of any reported uncertainty information. Conclusions should take due account of the reported measurement uncertainties.

9.4.3.2 **Assigned value and uncertainty**

Value assignment should use appropriate statistical procedures. The procedure used should be valid for the particular data set.

Note Validation of statistical procedures can include evidence of a sound theoretical basis (usually by reference to appropriate literature), known performance under the expected conditions of use and assumptions or conditions which can be shown to apply to the data sufficiently for the purpose at hand.

Instruction on the use of two commonly used procedures, the mean and weighted mean, is given in A.2.4.

The uncertainty of characterization can be estimated either by using the uncertainty statements submitted by the laboratory or from the submitted data, ignoring the uncertainty statements made by the laboratory, or from a combination of both. More information is given in A.2.5.

9.4.4 **Single-laboratory multi-method studies**

In some cases, organisations have invested an exceptional amount of effort in method development, such that the metrological control of the measurement procedures approaches that of reference measurement procedures. In such cases, data sets from only a few of these measurement procedures, given that their measurement principles are sufficiently different, can be sufficient for characterization. Under these circumstances:

a) the RMP is likely to have access to the complete quality assurance and validation data, which should be taken into consideration for the technical evaluation;

b) the number of data sets is small. Therefore, more emphasis should be put on the assessment and proper treatment of measurement uncertainties. The evaluation should rely on the assessment and use of measurement uncertainties associated with each measurement procedure.

Where results agree within the claimed uncertainties, the weighted mean (A.2.4) and corresponding uncertainty may be used. Where apparently valid results do not agree well within the claimed uncertainty, one should carefully reconsider whether the metrological control of the measurement procedures is indeed

sufficient for this approach. If this is confirmed, the effect of the excess dispersion of results should be allowed for in the certified value uncertainty.

Note: Approaches that make allowances for excess dispersion include those of Mandel and Paule, Vangel and Ruhkin, Birge and others. Details can be found in Reference.

9.5 Characterization of an operationally defined measurand using a network of competent laboratories

9.5.1 Concept

This approach is applicable to the production of RMs certified for operationally defined measurands. As in this case the measurement procedure defines the measurand, demonstration of absence of a laboratory bias is often only possible by combining data from several laboratories. In addition, the defining procedure is often relatively imprecise and the only practical means of obtaining a small uncertainty is to average many results from different laboratories.

This approach is largely similar to that described in 9.4, with the exception that all laboratories apply the same procedure.

The assumption is again that a number of laboratories exist that can perform the measurement in question equally well. The approach aims at randomization of all influence factors within the limits set by the measurement procedure.

9.5.2 Study setup

A well-described measurement procedure should be chosen. This should be a published standard method, ideally an internationally agreed procedure (e.g. ISO, ASTM, AOAC or IFCC). Participants should be instructed to follow the procedure exactly, allowing only those variations that are permitted within the procedure.

Note 1: Any modification of such a procedure agreed by all participants (e.g. tighter specifications for some parameters) results in principle in a modified procedure and the measurand's identity is then defined by reference to the modified procedure.

Note 2: Preliminary studies can show unintended departures from the standard procedure, which can be corrected before proceeding to characterization in order to ensure adherence to the standard procedure.

Note 3: Quality control samples can also be used in this case to demonstrate that a particular instrument fulfils all specifications.

9.5.3 Evaluation

In the case of operationally defined measurands, the defining procedure is (by definition) unbiased and it is then necessary only to consider possible laboratory bias and within-laboratory effects in an uncertainty evaluation.

The approaches described in A.2 apply for the evaluation of results.

9.6 Purity

9.6.1 General

Pure substances constitute the primary measurement standard and ultimate source of higher-order metrological traceability for most traceability chains in chemistry, thermometry and calorimetry in general and for the certification of solution and matrix reference materials in particular. The adjective “pure” refers to an idealised situation: no substance is 100 % pure, there will always be impurities present at some level. The appropriate certification of substances for purity is thus an essential cornerstone of traceability in chemical measurement.

Pure substances are an important class of CRMs in their own right. They are used by laboratories either to disseminate higher order traceability to calibration standards used in measurement procedures, or in the certification and production of other CRMs, such as solutions or gas mixtures.

The purity of substances can either be determined directly (by measuring the amount of the substance in question) or indirectly by subtracting the mass or mole fractions of all impurities from 100 %.

When characterizing the purity of a material, the identity of the material should additionally be confirmed.

9.6.2 Direct determination of purity

In some cases, the mass or mole fraction of the substance in question can be determined directly. Suitable methods can include coulometry, titrimetry and calorimetry (freezing point depression). In the case of organic analytes, the use of the technique of quantitative NMR for the direct certification of the purity of reference materials is increasingly being implemented.

Methods requiring calibration with the substance in question (e.g. HPLC, GC, ICP-MS or AAS) can in principle be used for purity assignment, but they are secondary measurement procedures. Since they require a standard of known purity, the application of such methods for direct determination of purity is often limited to the assignment of values to working standards.

The purity determined by the procedure used is adopted as the assigned value and the uncertainty of the purity determination is adopted as u_{char}.

Confirmation of these values by independent measurements is highly recommended.

9.6.3 Indirect determination of purity

Purity can be determined by difference, using a set of orthogonal analytical techniques capable of detecting and quantifying all the major classes of impurities in the material, as follows:

a) a suitable range of possible impurities are investigated, often including residual organic solvents, water, inorganic and organic impurities. The types of impurities to be investigated are often informed by the manufacturing process for the substance;

b) the amount of each of the possible impurities is determined in the substance to be certified;

c) the purity of the main component is computed by difference.

The measurements necessary to determine the impurities can be challenging, since most impurities will be close to the detection and/or determination limits or can be difficult to resolve in the case of impurities closely related in structure to the main component. Furthermore, different measurement methods can give results in non-compatible units (mass fractions for volatiles; mole fractions for total impurities by calorimetry), which makes the combination of such results in a strict metrological sense impossible if the structures of the impurities are not known. Quantification of each impurity against specific calibrants is ideal, but can be impractical or impossible if sufficient resources or appropriate reference materials are not available. In this case, appropriate allowance has to be made for the uncertainty introduced as a result of assumptions regarding the identity and response factors of individual impurities.

Note: The ICH harmonized tripartite guideline Q3A "Impurities in new drug substances" requires that impurities above 0,05 % (depending on the daily uptake of the substance) be identified.

Although high relative uncertainties can be obtained for the quantification of individual impurities, provided the absolute level is small, the contribution to the uncertainty of the final value for the main component is usually low.

The model for the certified value y_{char} of the amount of substance or mass fraction of the main component *y* as a function of *k,* impurities with amount of substance or mass fractions *wi* is given by Formula (14):

$$y_{\text{char}} = 1 - \sum w_i \qquad \text{(Formula 14)}$$

Assuming independence among measurements of the mass fractions of the impurities (which is often the case), the combined standard uncertainty associated with the amount-of-substance or mass fraction of the main component is

$$u^2_{\text{char}} = \sum u^2(w_i) \qquad \text{(Formula 15)}$$

where $u(w_i)$ is the standard uncertainty in w_i. It frequently happens that some of the impurity amount of substance fractions or mass fractions *wi* are zero, due to the fact that either these impurities are truly absent, or that their levels are below the detection limit of the measurement procedure. Where a value for an impurity is below the detection limit, the value is sometimes set to zero and other times another value is assigned, often related to the limit of detection, with an associated uncertainty.

The evaluation of the uncertainties can also be complicated by the proximity of physical limits (amount of substance and mass fractions are only defined between 0 and 1), which can create additional problems, including estimates for some contributing impurity classes that include nominally negative values.

9.7 Identity

9.7.1 Materials certified based on provenance

A reference material may be characterized based on knowledge of the origin of the material, i.e. the provenance of the material.

To support characterization based on provenance, the RM producer should obtain documentary or other evidence of the origin of the material that shows an unbroken chain of evidence from origin to final packaging. The documentation should be maintained for the lifetime of the material.

RM producers should have procedures in place to ensure that handling of the material (including sampling, homogenization, packaging, storage, etc.) prevents contamination by other materials and does not change the response of typical test methods for which the material is intended.

Whenever possible, RM producers should undertake experimental verification (including measurement, expert inspection or qualitative testing, as appropriate) to confirm the identity assigned using provenance.

Example: DNA extracted from a bacterial culture grown from a single bacterium, which in turn has been isolated from a bank of reference strain, could be certified based on provenance, subject to confirmatory checks for contamination.

9.7.2 Materials certified for identity based on measurements

9.7.2.1 General

When characterizing the identity of a substance based on measurements, several aspects should be borne in mind, including:

a) Identity is usually not a measurement result, but a conclusion drawn based on measurement results from one or several methods. For example, chemical shifts and the heights of peaks in an NMR spectrum, or a combination of colour, melting point, molar mass, etc., can inform an assignment of identity. While measurement uncertainties can be assigned to the individual measurement results, combining them to give any numerical indication of uncertainty in the identity (for example, a probability that the assigned identity is correct) is not straightforward.

Example 1: Identification using DNA sequencing illustrates the difference between uncertainties in identity and uncertainties associated with measurement results. The DNA sequence is a result of a sequence determination experiment, and the probability of base pair and other errors in the sequencing as well as the presence of mutation differences between different DNA molecules can in principle be estimated. However, identity of a biological species can often be established with considerable confidence at relatively low percentage of homology with a reference sequence. Individual sequencing errors therefore might not materially affect the assignment of identity.

b) A CRM certified for identity is in practice only useful if the error probability on the conclusion is negligible.

c) Slight heterogeneity and instability of the material does not necessarily change the conclusion of identity. The guiding principle for the assessment of homogeneity and stability is applicability of the material, i.e. whether it still allows unequivocal identification.

d) Different substances can share the same properties for the identification methods chosen. Information on the source of the raw material and on the processing steps of the material to be characterized is therefore vital for the certification of identity.

e) As with any material, the project planning should establish a clear definition of the need for identity information based on the intended use of the material.

Example 2: For DNA, the intended use could require only a statement of species identity, a complete sequence, or additional information on the degree of methylation.

Note Identity is sometimes determined by expert judgement (e.g. for asbestos fibres or microbial species). However, this judgement is usually based on observations and comparison with specifications. Expert judgement based on observations falls within the scope of this clause.

9.7.2.2 **Specification**

Testing for identity of a material involves comparison of a set of measurement results on that material with specifications (for example, melting point range; percentage of homology with a reference DNA sequence) for these measurement results.

Example: An organic polymer material might be identified based on comparison with a reference infrared (IR) spectrum using the following criteria:

— all peak frequencies in the reference spectrum are matched within 3 cm−1;

— relative peak intensities match the reference spectrum within 5 % absorbance;

— no peaks in the reference spectrum are absent;

— all peaks present in the candidate RM spectrum are present in the reference spectrum.

Sources of specifications can include internationally recognized compendia (e.g. Pharmacopeia sources and other collections of reference data. Such information can change outside the control of the RM producer. RM producers should therefore clearly state the specifications used for the assignment of identity, either as a set of values or as a dated reference on the certificate to an external specification.

When compiling specifications, RM producers should compare various literature data, establish the range of reported values and establish and document specifications for each measurand reflecting the ranges and reliability of the information used. Preference should be given to reference data which have undergone peer review.

9.7.2.3 **Characterization of identity by a combination of methods**

This approach is especially suitable for defined chemical substances of a small to medium molecular mass.

A number of methods should be chosen that probe different properties of the candidate reference material. Frequently used methods include, for example, determination of melting point, molar mass, UV, IR, NMR and mass spectra. Together with information on the raw material and its processing steps and the sampling and transport to the RM producer, the collection of methods should be sufficient to establish the identity of the material beyond any reasonable doubt. If detailed published specifications (e.g. Pharmacopoeial criteria for identification) exist, the choice of methods may be restricted to those listed in these specifications.

Note 1: The nature and number of methods required to establish identity varies with the number of potentially similar products (e.g. there are more organic than inorganic substances) and the information on the origin and processing steps.
All test and measurement procedures used should be properly validated and the results should fulfil the requirements for traceability laid out in 9.2. Where available, appropriate control materials should be examined alongside the RM, during characterization.

The results of each of the tests and measurements made should be compared with the specification for the proposed substance. Published procedures for such comparisons should be followed, where available. Where no such prescribed procedures exist, measurement results should not differ from any of the specified values when taking the combined uncertainty of measurement and specified value into account.
If the results agree with the specification, identity is established with a negligible uncertainty.

Note 2: A judgement on whether the accumulated measurement and provenance information is sufficient to establish identity beyond reasonable doubt is somewhat subjective. RM producers are therefore strongly encouraged to establish a system of peer review.

9.8 **Presence/absence**

Presence/absence is an example of a quantitative measurement that is evaluated in a qualitative manner. Results above a predetermined threshold are classified as “presence”; results below are classified as “absence”.

NOTE 1: Many measurements are evaluated as present/absent but are never quantified. Even for these methods, however, there is usually a limit for the response to be regarded as indicating “presence”. Existence of such a limit indicates the quantitative nature of the measurement despite the qualitative evaluation.

Quantitative evaluation of the measurements is one solution to this problem. Although the measurement uncertainty is frequently high (which is the reason for the qualitative evaluation), this approach has the advantage of being conceptually simple. The simplest case is characterization of a material for the absence of a substance for which quantitative methods exist (e.g. a contaminant in a foodstuff). In this case, all measurements on the material should give results below the critical value for declaring a substance present and the certified value is stated as “< L_d”, with L_d being the limit of detection. If test results are not quantitative, all measurements should provide the result “absent” to certify a material for the absence of a certain substance and the reference value in this case is stated as “absent”. Also, the limit of detection of the measurement procedure should be given.

Note 2: The term “Limit of Detection” is used in its IUPAC definition as “smallest measure that can be detected with reasonable certainty for a given analytical procedure”. This refers to the (true) concentration where one is reasonably certain to detect a substance if it is present and corresponds to CCβ (in European Commission Decision 2002/657EC and to the “minimum detectable value of the net state variable” (as defined in ISO 11843-1. For a given procedure, this limit depends on the number of replicate measurements.

For CRMs, the uncertainty statement should state the confidence level for any upper limit given for the concentration.

If several measurement procedures are used, and the results all agree, the limit of detection of the most sensitive procedure may be used as the certified value.

Example Three different measurement procedures give results stated as < 2 mg/kg, < 5 mg/kg and < 4 mg/kg. As all results agree, the certified value is set as < 2 mg/kg. For an example, see Reference.

Note 3: Use of different procedures and/or laboratories can help to avoid misinterpreting losses during the analytical procedure as absence. Furthermore, inclusion of information on the processing of the material can be used to support the statement of absence of a certain substance.

Note 4: It can be necessary to declare a substance to be present if the result is above a critical value, even if it is below the limit of quantification. See for further guidance ISO 11843-1.

9.9 Ordinal scales

Some properties are expressed on an ordinal scale, which usually places items in ordered classes. Examples are the Mohs hardness scale or skin irritation classified as no response/moderate redness/significant irritation/severe reaction. These scales are often defined by reference to a particular method of classification. The only possible characterization approach in that case is therefore characterization by several laboratories using the same method.

In many cases, an RM will only be useful if it is put into one class without any disputes. To achieve this, all technically accepted measurements by all participating laboratories should put the material into the same class.

If some results deviate and the deviation cannot be explained by technical errors, no class can reliably be assigned. It can, however, be useful to give the median and/or the mode of the technically valid results as an information value.

9.10 Qualitative properties

Materials can be characterized for qualitative properties such as colour, odour or shape. In some cases, these properties can be quantified and are in practice often used in this quantified form. Examples are the shape parameters of particles or colour according to the Hunter system. This transforms the problem to the characterization of a method-defined measurand as described above. For colour especially, characterization of the absorbance/reflectance spectrum may also be considered.

9.11 Characterization of non-certified values

According to the definition of “reference material” and “certified reference material”, only certified values need to be accompanied by a measurement uncertainty and a statement of metrological traceability. Apart from the certified values, non-certified values (named, for example “indicative values”, “information values” or “informative values”) may be assigned, which, however, cannot be used as a reference in a metrological traceability chain.

As there is no requirement for uncertainty and traceability (i.e. no requirement for comparability) of such values, a wider range of approaches can be used for value assignment, including use of literature data about typical properties, circumstantial data from single laboratories or pooled data from several

laboratories. The closer the chosen characterization approach resembles an approach appropriate for certified values, the more reliable this assigned non-certified value will be.

It is recommended to give information on the origin of the non-certified value, and why it is not certified, to allow users to assess its fitness for purpose. While not required, traceability statements and statements of uncertainties increase the usefulness of these values.

Annex A

(informative)

Design and evaluation of studies for the characterization of a method-independent measurand using two or more methods of demonstrable accuracy in one or more competent laboratories

A.1 Study design

A.1.1 Selection of measurement procedures

When selecting measurement procedures, variation of among others the following aspects should be considered:

- sample preparation, for example grinding/milling, extraction or clean-up steps;
- sample introduction and/or separation, for example using LC or GC;
- quantification principles, for example molecular or atomic absorption, mass spectrometry, flame ionization or fluorescence;
- calibration procedures, unless one approach has clear advantages, because of its metrological rigour or because of achieving lower measurement uncertainties.

In many cases, variation of all aspects will be impossible. In these cases, the maximum possible variation should be sought. For example, if gas chromatography is the only available separation technique, then the study should at least aim to include different injection techniques, different columns and temperature programs and quantification by different detectors.

The RM producer should require that all measurement procedures used in the campaign are properly validated and that a reasonable estimate of the measurement uncertainty can be provided.

To allow laboratories the free choice of measurement procedures while ensuring the necessary variation, the RM producer should obtain information about the measurement procedures applied by the participants before the start of the study to obtain the necessary range of procedures. If required, a targeted search for laboratories offering specific methods should be performed to avoid receiving results obtained by only one method.

A.1.2 Choice of calibration standards

An important decision is whether all laboratories should use the same calibrator or whether laboratories should be given free choice of the calibrator. Using a single calibrator reduces variation caused by different calibrators from different suppliers. On the other hand, any bias in this single calibrator will translate into the same bias in the certified values. Therefore, use of a single calibrator requires very careful characterization of this calibrator, requiring in many cases independent confirmation of purity or composition. Allowing laboratories, the free choice of calibrator is logistically easier, does not require tests for independent confirmation and allows laboratories to apply their procedures unchanged, but means that some way of checking the appropriateness of the calibration should be included in the study. As a general guideline:

- for well-established measurements, where experience shows that the quality of available calibration standards is sufficient, giving laboratories the free choice of standards is usually preferable;

— in cases where there is significant doubt about the quality of standards on the market, the efforts needed to characterize a common standard are often justified.

In some cases, different producers of commercial standards obtain their pure material from the same company. It is therefore useful to establish whether the original sources differed.

A.1.3 Selection of laboratories

Laboratories should be selected based on demonstrated competence. Appropriate evidence for the demonstration of competence may include the following:

- results from proficiency tests;
- results on independent CRMs (possibly distributed as quality control materials together with the candidate CRM);
- method validation data;
- a full and credible uncertainty budget;
- previous participation in other RM certification campaigns for the same measurand; and
- third party assessment of conformance with ISO/IEC 17025 or other relevant standards for the determination of the measurand in question.

The performance of externally assessed laboratories can differ in the same way as other competent laboratories. It is therefore prudent to obtain information on performance in addition to evidence of third-party assessment of conformance with ISO/IEC 17025.

The RMP should ensure that the measurements in each laboratory are performed in accordance with ISO/IEC 17025. In particular, the provisions of ISO/IEC 17025 regarding competence of staff, calibration of equipment and authorization (official release for use of methods and results should be met.

In the absence of independent assessment, information on the extent of the laboratory's quality systems should be obtained.

NOTE 1 Potential gaps in fulfilling the requirements of the respective standard can sometimes be filled by the RM producer (e.g. an RM producer can archive the laboratories' raw data, if they do not have an archiving system).

NOTE 2 Obtaining calibration certificates for each and every instrument is in many cases impractical. Agreement of results on quality control samples can be used as demonstration of sufficient calibration of all relevant input factors.

A.1.4 Number of independent data sets

The number of participating laboratories is less important than the number of independent data sets. A single laboratory might be able to provide several data sets, all obtained by independent measurement procedures. The remainder of the discussion focuses on data sets, regardless of whether each data set was provided by a different laboratory, some laboratories provide more than one data set or all data sets are provided by the same laboratory.

Complete independence of results is difficult to achieve if measurements are performed in a single laboratory. The RM producer should critically review the variation of all critical steps as outlined in A.1.1 to check whether sufficient method variability is present to demonstrate absence of bias for each individual step. This includes checking whether the same critical chemicals, equipment, calibrators, etc., were used by the various measurement procedures. The organizer should also remind the laboratories at the onset of the study not to censor data, i.e. not to suppress/change data from one procedure without notification after a crosscheck of results between the various procedures.

The RM producer should set a documented minimum number of technically valid results for which value assignment will be considered. The number of data sets should be large enough to provide an adequately small uncertainty in the estimated value after allowing for the possibility of failure to report, exclusion of results for technical reasons and the statistical evaluation intended.

For interlaboratory studies using a network of testing laboratories, the characterization should include five or more participants providing technically valid data.

NOTE : A characterization uncertainty less than one third of the interlaboratory reproducibility standard deviation requires at least nine participants unless laboratories are selected for exceptional performance.

The following considerations affect the number of data sets required in order to achieve the desired uncertainty for certified values.

- **Uncertainty required**: The uncertainty of assigned values usually decreases with the number of technically valid data sets, requiring more data sets for smaller uncertainties.
- **Technical difficulty**: The less well established or the more technically challenging a measurement is, the larger the between-data set variation can be expected to be.
- **Likelihood of technically invalid results**: Even experienced laboratories can deliver technically invalid results which cannot be used for certification. Such results are more likely for unfamiliar materials, new or modified measurement procedures, challenging measurements or unusual reporting requirements. The number of participants or (for single laboratory studies) independent measurements should be increased where the risk of technical errors is higher.
- **Reproducibility/repeatability ratio**: Where between-data set variation is known to be the primary source of variation, preference should be given to a larger number of data sets rather than higher number of replicates for each data set.
- **Statistical evaluation**: Different data treatment methods can require larger numbers of observations to provide good numerical stability and/or achieve sufficiently small uncertainty.
- **Validation results from a CRM**: Results of consistent high quality obtained from one or more similar CRMs, used for quality assurance at each laboratory, serve to demonstrate the validity of all data sets and to provide information on bias among laboratories and measurement procedures.

A.1.5 Number of units and replicate determinations

The number of units of the candidate CRM sent to each participant, the number of replicate determinations performed by each participant and the condition of these determinations are determined by practical as well as evaluation considerations.

- If the variation between individual units of the RM is large, single measurements on several different units are preferable to several replicate measurements on a single unit. If contamination, breakage or heterogeneity are not an issue, sending a single unit is sufficient.
- In the absence of reliable uncertainty evaluations by the participants, requesting measurements under conditions of intermediate precision can provide an indication of the reliability of the participants' results or a check on the reliability of the participants' uncertainty estimates.
- If each laboratory receives more than one unit, more measurements can be made on the remaining unit(s) in case of breakage of one unit, which eliminates the need for a new dispatch.

A.1.6 Quality control materials

Inclusion of additional samples for quality control has been found to be highly beneficial. Results on these samples can identify technical problems and aid the technical evaluation.

- RMs, in particular natural matrix RMs and quality control (QC) materials, may be used to demonstrate the validity of the measurement result when measured alongside the unknown material to be characterized.
- Spiked materials, spiked blanks, etc., may be used to check parts of the measurement procedure or to assist in the process of assigning values to a material.
- Blank matrix materials, blank extracts, etc., may be used to demonstrate that the measurement procedure provides a result not significantly different from zero when the characteristic of interest is not present (as often done in composition measurements), or to establish a correction or correction factor together with the uncertainty of the correction factor.

NOTE Sometimes CRMs used for quality control in an interlaboratory study are supplied without the original label to avoid identification. However, as the number of reliable CRMs is limited, experienced laboratories can recognize the material from the visual appearance and/or the values.

A.1.7 Instructions for participants

Guidelines to participants should contain:

a) a clear outline of the goal of the study;

b) instructions to refrain from comparing results with other participants, including the reasons for discouraging collusion (that is, cooperative exchange of information);

c) the number of units to be tested;

d) the number of replicate determinations to be performed;

e) any restrictions or specific details of measurement procedures to be used; for example, any need for prior drying and moisture correction;

f) the minimum test portion size;

g) requirements with respect to quality and traceability of the measurement results;

h) the time schedule (distribution of samples, delivery of results);

i) the mode of dispatch;

j) instructions for intermediate storage of samples;

k) specific instructions for sample treatment, if applicable;

l) instructions on quality control measures to identify potential bias; and

m) information on the producer's policy on identification of laboratories and use of data; for example, whether laboratories will be identified, whether results will be identified with a particular laboratory and whether the results may be used for purposes other than the characterization study.

NOTE 1 A meeting with the laboratories/groups involved (prior to distributing the samples and performing the measurements) can help all parties involved to align all actions to be carried out during the collaborative study, and to discuss possible problems and/or pitfalls.

In an interlaboratory study the RM producer should take reasonable steps to prevent collusion between laboratories, including but not limited to b) above.

NOTE 2 Different labelling of materials for each participant can make it harder for participants to compare results.

A.1.8 Reporting

The use of preformatted reporting forms can be useful as it has the advantage of structuring the report and (if transmitted electronically) allows copying of the results, which can reduce transcription errors in the RM producer's collation of results. Disadvantages of preformatted reporting forms are that they often force laboratories to depart from their usual reporting practices, which can lead to transcription errors. If reports are submitted electronically, the requirements of ISO 17034 on the integrity of electronic records, especially of reports of test results, should be adhered to.

NOTE When reports are submitted in spreadsheet form, unintentional alteration can often be prevented by the use of 'locking' or 'protection' facilities incorporated in the spreadsheet software.

Laboratories can be requested to report individual results (not only averages over all samples), regardless of whether an uncertainty statement is reported or not, although reporting of an average and an expanded uncertainty and its coverage factor can be sufficient.

Where there is an option for correction of a known procedural bias, such as extraction recovery, the RM producer should state clearly whether results should be corrected or not. The RM producer may also require participants to report bias checks (e.g. from spikes) and use these to correct results for detected bias. Where a correction is applied by the participant, any reported uncertainty should include the uncertainty associated with the correction.

Participants should be instructed on how to report results near detection limits, if such results are likely to occur. Results reported as "less than" make statistical evaluations more difficult. On the other hand, reporting of results near detection limits contradicts many laboratories' quality procedures. Where results near detection limits are likely, RM producers should either require laboratories to report the observed (including negative) results instead of, or in addition to, their normal reporting, or should adopt statistical

procedures that allow for “left-censored” results such as “less than” statements or results restricted to values above zero.

Instructions to participants should specify the measurement units and number of significant digits to be reported for quantitative results.

It is recommended that an outline of the measurement procedure used is reported in sufficient detail to permit an understanding of all stages in the measurement process (e.g. in chemical analysis, the digestion/extraction of the sample and separation of the analytes of interest, clean-up, and quantification). Participants should be requested to give literature references, where applicable.

A.2 Evaluation

A.2.1 General considerations for evaluation

In the course of evaluation, anomalies can arise that require communication with the participant concerned. The producer may contact participants to assist in the investigation of anomalies at any stage of the evaluation process. If a participant is contacted, it is recommended that initial contact should not specify the nature of the anomaly (for example, the direction of deviation of the results); rather, the participant should initially be invited to investigate and report any errors discovered.

If data sets from more than one measurement procedure are provided by a single laboratory, initial inspection should consider the data sets individually (that is, as if independently reported by different laboratories). The RM producer should nonetheless take account of all data sets submitted by a laboratory when drawing conclusions about which of the data sets to retain when anomalies are found.

A.2.2 Initial screening

A.2.2.1 General

Information from each participant should be examined on receipt or as soon as practicable after receipt.

Initial examination of individual participant results should check for evidence of basic reporting or procedural errors such as missing data (including any requested information that is absent); incorrect numbers of replicates; inappropriate conditions of measurement (for example, repeatability versus reproducibility conditions); incorrect identification of test items (e.g. through accidental mislabeling) and incorrectly reported units of measurement. Apparent errors at this stage should, where possible, be referred promptly to the participant for checking and possible correction (see A.2.1).

Unexpectedly high or low results or uncertainties can also be apparent on receipt and may be referred to the participant for checking at this stage.

A.2.2.2 Technical evaluation

Further technical examination to identify potential problems may include (but is not limited to) grouping results by techniques (measurement procedure and principle, sample pre-treatment methods, etc.) or the calibration technique used. In addition, comparison of the expanded uncertainties with the confidence interval of the mean of the submitted results gives an indication of whether the stated uncertainty is realistic, as the expanded uncertainty should be at least as large as the confidence interval.

Technical examination of individual participant results should, as far as possible, check for evidence of errors in procedure such as: reported use of an inappropriate measurement procedure or pre-treatment

procedure; inappropriate calibration; inappropriate conditions of measurement (for example, repeatability versus reproducibility conditions) and incorrect units of measurement. Where measurement uncertainty is reported, the examination should check for unusually high or low uncertainty compared with typical expectations and, where uncertainty budgets are available, for omission of significant contributions to uncertainty or inappropriate uncertainty evaluation methods.

Technically invalid results should be removed from the data set or corrected, by repeating the measurement, if possible and necessary.

NOTE 1 A technically invalid result is not necessarily an outlier nor is every outlier necessarily technically invalid. A result can fall well within the range of valid results, even when it is evident that the conditions, under which the result was obtained, were not in good order. Conversely, a result deviating significantly from all other results can be the only technically valid result of the data set.

NOTE 2 Appropriate choice of statistical procedures for value assignment can allow useful value assignment even when reported uncertainties show evidence of, for example, under-estimation. Reference provides further guidance on such procedures.

A.2.3 Statistical evaluation

A.2.3.1 General principles for statistical evaluation

Characterization by a collaborative study or by multiple measurement procedures aims at randomization of bias between data sets. Statistical evaluation typically assumes that the true value of a measurand corresponds to the true value of a population parameter, usually the population mean.

Different procedures intended to estimate the value of a particular measurand – whether the measurand is operationally defined or not – can be systematically biased as well as showing laboratory specific bias per data set. The possibility of between-method differences should normally be considered in evaluating measurement uncertainty.

Where measurement uncertainty is reported, statistical evaluation should check for unusually high or low measurement uncertainty, uncertainty/location anomalies such as results far from any central estimate compared with their reported uncertainty, and any evidence of generally inadequate uncertainty evaluation (for example, greater dispersion than accounted for by reported uncertainties). Anomalies related to reported measurement uncertainties should be resolved where possible, for example by referral to participants for checking and possible correction.

A.2.3.2 Distributions

Finding appropriate estimators for the expected value is closely linked to the (either assumed or determined) underlying distribution of values.

Determining a probability density function from a data set requires significantly more data than can practically be obtained, whereas checking for consistency with an assumed distribution and calculating parameters from it (e.g. average of a normal distribution) is possible with the number of data sets usually available in characterization studies.

The RM producer should therefore check whether there is evidence of deviation from the assumed distribution using, for example, visual methods (histograms, kernel density plots and normal probability or, more generally, Q-Q plots) or statistical checks for departure from particular distributions, including tests for normality or determination of skewness and kurtosis. An approximately normal distribution of data sets is often observed for results well above the limit of quantification; other distributions include Poisson

distributions (e.g. microbe counts) or a Weibull distribution (e.g. mechanical failure of ceramics). The selected distribution should be in agreement with the reported data as well as with the theoretical and historical knowledge of the measurement in question. If these differ significantly, no value should be assigned unless technical reasons for the unexpected distribution can be given.

EXAMPLE Theoretical considerations as well as a multitude of interlaboratory comparisons indicate that results for trace elements in soil follow normal distributions (unless the level is close to the limit of quantification). Deviation of the observed data from normal distribution (e.g. tailing) indicates technical problems. If it is not known whether the problem lies with the majority or with the tails, no value is assigned.

In some cases, the results can be transformed so that they become approximately normally distributed. Some commonly used transformations include logarithmic, square root and exponential forms. There should be a technical basis for such a transformation, as deviation of the results from the expected distribution may indicate technical problems.

A.2.3.3 Outliers

Outlying results can occur at all levels of a collaborative study: single observations, subgroups of observations (e.g. grouped per bottle), or the results from complete methods/laboratories can be observed to be outlying. Outliers may be identified by, for example, appropriate outlier tests for outlying means and variances, graphical inspection of raw data, and use of Mandel's h and k statistics

Outlying observations or mean values should not be removed solely on the grounds of a statistical outlier test, but may be removed if there is a technical reason to do so.

NOTE 1 Technical reason include inadequate calibration, inadequate measurement procedures, use of inadequate reagents, failure to account for interferences and deviation from the certified value of an independent quality control material.

NOTE 2 Outlier tests usually ignore measurement uncertainties. An outlying data set can agree with the other data when the respective uncertainties are taken into account.

NOTE 3 Data points, with unusually large uncertainty, can be removed on technical grounds, if they agree with the other results within their uncertainties, and if the uncertainty is so large compared with the other reported uncertainties that it indicates a technical problem. They can also be retained, because they agree with the rest of the results.

NOTE 4 Data sets that show a high outlying variance can indicate a lack of method repeatability or lack of intermediate precision, which can justify rejection on technical grounds.

NOTE 5 Different measurement procedures may differ in precision and it can be important to retain data sets for a relatively imprecise procedure in order to retain a representative collection of procedures.

NOTE 6 A special case of extreme variance is a set of results having zero variance. This can arise when laboratories report too few significant digits. This can be prevented by appropriate instructions to participants (A.1.7) or corrected by reference to the participant. Use of the mean or median of such a group of identical data can also be valid, for example where between-group effects dictate the use of group means.

A.2.3.4 Robust statistics

Robust statistics provide a large collection of statistical methods that explicitly allow for the presence of outlying values in an otherwise approximately normally distributed data set. Typically, robust methods

assign weights that decrease with the distance from the main body of the data. Robust methods exist for estimating the mean and standard deviation for simple outlier-contaminated data sets, as well as for many other parameters of interest. Robust methods also exist for other situations including, for example, sets of reported values with appreciably different uncertainties, or the analysis of data consisting of multiple replicates for each data set.

Robust estimators provide high resistance to the influence of extreme outlying values. For symmetric 'heavy-tailed' distributions (that include a larger proportion of values far from the mean than would be expected from a normal distribution), robust statistics typically provide unbiased estimates of the mean with lower variance than the simple arithmetic mean. This approach results in an unbiased estimate with smaller uncertainty than the arithmetic mean would give in the same circumstances. For data with extreme outliers, robust statistics can be a very considerable improvement over the mean. A short summary of useful robust statistical methods, together with conditions for their use in RM characterization and references to more detailed descriptions, is given in B.5.

NOTE The tolerance of robust statistics to extreme values additionally makes them useful for identifying outliers in larger data sets containing several extreme values.

A.2.3.5 Grouping ("clustering")

Statistical evaluation should check for the occurrence of grouping of results, for example along measurement procedure, calibrants, reagents or regions.

a) If the difference between means for different groups is statistically significant and is too large to permit a sufficiently small uncertainty for the intended use of the material, then no single property value can be assigned. Where grouping is along reagents/calibrants, the technical evaluation should check whether all of them are appropriate. Where the grouping is along measurement procedure, the producer may provide an assigned value for each measurement procedure.

b) If there are significant differences and the difference between the means of these groups is relatively small, one single value may be assigned. An additional uncertainty term accounting for the between-group variation should then be added to the uncertainty of characterization. There are several approaches to this estimation problem described in the literature.

c) If the difference between these clusters is large and there is no correlation of these clusters with measurement procedures or other technical explanation for the differences, no value can be assigned. A larger pool of results can be necessary to overcome the relatively poor agreement of measurement procedures available.

NOTE Visible grouping can arise from other causes, including chance (especially in small data sets), regional differences in application of a procedure or use of different calibration standards.

A.2.4 Assigned value (weighted/unweighted mean)

Where the data set means follow an approximately normal distribution and no weighting is applied, the unweighted arithmetic mean of the p data set means y_i is applied as assigned value y_{char}.

$$y_{\text{char}} = \frac{\sum y_i}{p} \qquad \text{(A.1)}$$

The mean value of individual results may also be adopted as the assigned value where differences between data set means are insignificant compared with the effects of variation within each data set.

A weighted mean is usually calculated using the general form of Formula (A.2):

$$y_{\text{char}} = \sum_{i=1}^{p} w_i x_i \Big/ \sum_{i=1}^{p} w_i \qquad \text{(A.2)}$$

Where *wi* is the weight applied to each data set mean (or, where a value and uncertainty are provided, to a single value) x_i.

The simplest choice of weights *wi* is given by Formula (A.3):

$$w_i = 1/u_i^2 \qquad \text{(A.3)}$$

where u_i is the reported standard uncertainty for the value x_i. This scheme should be used only when the reported uncertainties can be shown to be reliable and where it is clear that differences between groups can be wholly accounted for by the reported uncertainties. Where the uncertainties do not account fully for the observed dispersion of values x_i, alternative schemes should be used. Where reliable weights cannot be ascribed, the simple mean is often a useful conservative alternative.

If the results do not follow a normal distribution but can be transformed into normally distributed data, the data can be evaluated according to the following steps: transform the raw data; apply the calculations as in Formula (A.1); calculate the assigned value and confidence interval; apply the reverse transform to the assigned value and confidence interval. If a standard uncertainty is also required, either refer to statistical texts on the variance of distributions, or use the GUM to obtain it, bearing in mind that first-order error propagation can fail badly for relative uncertainties over 15 % and higher-order terms can be needed.

If the results do not follow a normal distribution and cannot be transformed into normally distributed data, a statistically sound approach that is consistent with the observed distribution should be applied.

A.2.5 Assigned uncertainty

A.2.5.1 Use of analysis of variance for uncertainty evaluation

Analysis of variance (ANOVA) may be used as a tool to process the data. The use of ANOVA can be particularly helpful when assessing uncertainty components such as the between-bottle homogeneity or the between-laboratory standard deviation. Otherwise, the mean of means may be computed for these strategies instead.

A.2.5.2 Uncertainty-based evaluation

It is theoretically possible to combine the results, including their uncertainties, into a single value (the property value) and a combined standard uncertainty.

Approaches described include weighting results by uncertainties, determining detailed expressions for the uncertainties, least squares fitting or splitting uncertainties into common and individual parts.

NOTE These approaches are possible in theory, but are often difficult to implement in practice and have so far rarely been used.

A.2.5.3 Evaluation without the laboratories' uncertainties

Where Formula (A.1) was used to calculate the certified value, where the data set means follow an approximately normal distribution and no weighting is applied, the standard deviation of the mean of the p data set means y_i can be applied as u_{char}.

$$u_{\text{char}} = \frac{s(y)}{\sqrt{p}} = \frac{1}{\sqrt{p}} \cdot \sqrt{\frac{\sum (y_i - y_{\text{char}})^2}{p-1}} \quad \textbf{(A.4)}$$

where s(y) denotes the standard deviation of the p data set mean values.

A.3 Use of collaborative studies for multiple purposes

A.3.1 There can be different purposes for interlaboratory comparisons, including value assignment of reference materials, evaluation of the performance of laboratories and evaluation of the performance characteristics of a measurement procedure. In general, a particular study is best used for only one of these purposes; to do otherwise can compromise one objective in favour of another, or confuse the purpose of the study for the participants. Nonetheless, it can be useful to consider combining characterization studies for RMs with other studies to save costs, providing that due care is taken to avoid the principal disadvantages and that certain conditions are met. A.3.2 provides guidance on the principal disadvantages; A.3.3 provides conditions for combination of such studies with RM characterization.

A.3.2 Potential incompatibilities or conflicts when combining PT or method performance studies with characterization studies include the following.

a) PT studies aim to assess the competence of a laboratory whereas participation in characterization studies is restricted to laboratories of demonstrated competence. A combination of a PT study with a characterization study might therefore assume the very fact of demonstrated competence for the purpose of characterization that should be assessed in the PT part.

b) The requirements of proficiency testing do not normally require extensive replication and rarely permit specification of equal replication by all participants.

c) PT results are typically treated as confidential and access to details of experimental methods cannot be guaranteed.

d) Participants often pay for participation in a PT study and the motivation for participation can sometimes be commercially driven. Participants are therefore often unwilling to adhere to the detailed study setup, requirements for traceability and quality assurance, calibration, provision of uncertainties, etc., required in a characterization study.

e) The results of PT can be used for demonstration of competence to potential customers, accreditation bodies and others. Participants therefore can be less willing to discuss freely and to admit to technical problems required in a characterization study for the technical evaluation of results.

f) PT studies usually assess laboratory performance in comparison with other laboratories or with an externally set criterion, whereas a characterization study aims at getting a good estimate of the true value and its uncertainty. This leads to different approaches in evaluation, especially in dealing with extreme values/outliers.

g) PT studies are typically open to any laboratory willing to participate. RM producers therefore often have little control over the measurement procedures applied by the participants, which can result in receiving results from only one procedure even if other procedures exist.

h) While feedback on the results for the purpose of checking anomalies cannot commence before a PT study closes, this information is required for following up apparent anomalies of results in a characterization study.

i) The evaluation of a PT study also focuses very much on statistics, whereas characterization studies place more emphasis on the technical evaluation.

j) Method performance studies evaluate the performance of a measurement procedure immediately after development, so there is little prior information on typical performance.

k) Method performance studies typically apply to only one measurement procedure and are therefore not suited for assigning values to method-independent measurands.

A.3.3 Because of these potential conflicts, where a reference material is to be certified using data collected from participants in a PT scheme the RMP should:

a) decide, before the start of a study, which subset of data from specified laboratories will be used for value assignment;

b) demonstrate the competence of these laboratories independently of this study, e.g. from performance in previous rounds of the scheme or by other means;

c) organize the study for these selected laboratories according to the criteria described in A.1.3;

d) evaluate the results of these laboratories according to the criteria laid out in A.2;

e) notify proposed participants that results may be used in a certification study and obtain permission to access technical detail.

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