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**Metrological Tools for the Reference
Materials and Reference Instruments of the
NIST Material Measurement Laboratory**

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Foreword

The National Institute of Standards and Technology (NIST), formerly the National Bureau of Standards, was established by the U.S. Congress in 1901 and charged with establishing a measurement foundation to facilitate U.S. and international commerce. NIST provides reference materials and reference instruments that are used to ensure the accuracy, metrological traceability, and comparability of measurement results in many diverse fields of science, industry, and technology. This document provides and explains the vocabulary used at NIST to define and describe the reference materials and reference instruments available to NIST's customers as well as documenting the methods used in developing these materials. The definitions and descriptions provided supersede those used in the original version of this publication, NIST SP260-136.¹

Scope

The NIST Material Measurement Laboratory (MML) serves as the U.S. national reference laboratory for measurements in the chemical, biological, and material sciences. MML activities include the development and dissemination of reference materials and reference instruments to assure the quality of measurement results. While other NIST operating units develop reference materials and reference instruments, MML produces the majority of NIST reference materials and, via its Office of Reference Materials, supports the production and dissemination of ALL of NIST's reference materials and instruments. The definitions and descriptions provided in this document apply to NIST's certified reference materials (CRMs) and reference instruments issued after the publication of this document.

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ABBREVIATIONS AND ACRONYMS USED IN MULTIPLE PARAGRAPHS

BIPM	International Bureau of Weights and Measures
CCQM	Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology
CIPM	International Committee for Weights and Measures
CRM	certified reference material
DI	designated institute
GUM	Guide to the Expression of Uncertainty in Measurement
ICP-OES	inductively coupled plasma optical emission spectroscopy
ILS	interlaboratory study
ID-LC-MS/MS	isotope dilution liquid chromatography tandem mass spectrometry
ID-MS	isotope dilution mass spectrometry
NIST	National Institute of Standards and Technology
NMI	national metrology institute
NTRM	NIST Traceable Reference Material
ORM	Office of Reference Materials
PCR	polymerase chain reaction
PS	primary standard
qNMR	quantitative nuclear magnetic resonance
RGM	Research Gas Mixture
RGTM	Research-Grade Test Material
RM	Reference Material (produced by NIST)
RMP	reference measurement procedure
SI	International System of Units
SRI	Standard Reference Instrument
SRM	Standard Reference Material
VIM	International Vocabulary of Metrology
XRF	X-ray fluorescence spectrometry
24R,25(OH) ₂ D ₃	24R,25-dihydroxyvitamin D ₃
25(OH)D ₂	25-hydroxyvitamin D ₂

1. Introduction

NIST's mission is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve quality of life. One way in which NIST fulfills this mission is through the delivery of reference materials and reference instruments. NIST develops, documents, and delivers these reference materials and reference instruments in accordance with international standards and guidelines^{2,3,4,5} as described in NIST's Quality Management System for Measurement Services.^{6,7} Techniques and methods used at NIST for characterizing measurement procedures and evaluating the chemical and physical properties of materials are critically examined. Potential sources of bias and variability in these processes are addressed.^{8,9} Details of NIST's processes are documented in publicly accessible NIST Special Publications or in refereed scientific and technical journals.

This publication describes the metrological tools provided by NIST's Material Measurement Laboratory (MML) in the form of reference materials and reference instruments. Figure 1 displays the metrological validity and traceability hierarchy of these tools; note that links are provided for terms used throughout. See Section 1.2 for in-depth discussions of the reference material tools, Section 2 for definitions of terms, and Section 3 for descriptions of how property values are assigned to these tools.

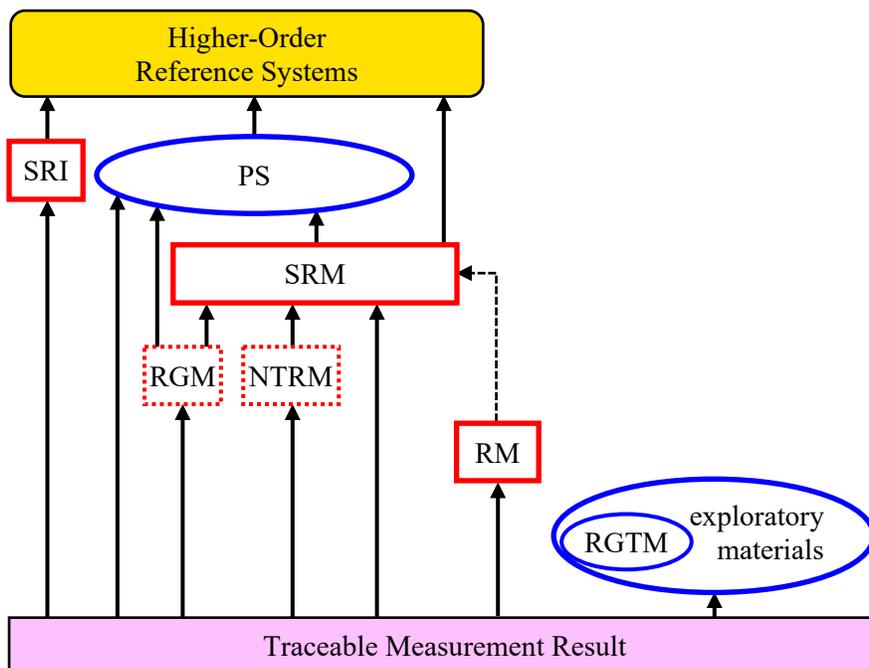


Figure 1. Traceability Hierarchy Among NIST's Measurement Tools

The [Standard Reference Instrument](#) (SRI), [Standard Reference Material](#) (SRM), and NIST's [Reference Material](#) (RM) measurement tools (solid red rectangles) are available for customer purchase. The [Research Gas Mixture](#) (RGM) and [NIST Traceable Reference Material](#) (NTRM) tools (dotted red rectangles) are produced in collaboration with industrial partners and are used by them to provide services to their customers. The [primary standard](#) (PS), [Research-Grade Test Material](#) (RGTM), and other [exploratory materials](#) (blue ovals) are used by NIST to support its own measurement procedures. Arrows indicate linkages among and between tools and the traceable measurement results. [Metrological traceability](#) linkages and confidence in the metrological validity of the assigned values improve from bottom to top. The dotted arrow indicates that the assigned values for RMs may or may not be traceable to SRM values. Results linked to RMs, RGTMs, and other exploratory materials are suitable for between-method [harmonization](#), within-method [precision](#), and within-method stability assessment. Results linked to SRIs and PSs are, in addition, suitable for method [calibration](#) and [validation](#). Experience gained from RGTMs and other exploratory materials is intended to contribute to the development of higher-order reference materials.

1.1. Standard Reference Instruments (SRIs)

Standard Reference Instruments (SRIs) are devices that have been designed and validated by NIST and are then sold to qualified customers. SRIs transfer to these customers the ability to obtain traceable results when [metrological traceability](#) cannot be adequately established through [reference materials](#). Some SRIs allow customers to directly realize an International System of Units (SI) unit (i.e., to experimentally establish the value consistent with the SI definition of the unit). SRIs are issued as “SRI 6xxx” where “xxx” is a unique series of three digits.

As shown in Figure 1, measurement results produced using an SRI are directly linked to [a higher-order](#) reference system. Such direct metrological traceability minimizes the [uncertainty of measurement](#) results. While ideally all measurements could be made using SRIs, an SRI is economically feasible in practice only when artifact reference materials or existing calibration services cannot provide [fit-for-purpose](#) calibration of less specialized measurement devices. Most SRIs are used for physical measurements requiring extreme [accuracy](#) or for [measurands](#) that are not amenable to being captured in a container. MML currently provides the following SRIs:

- **SRI 6005a and 6005b Polymerization Stress Tensometers**^{10,11}
 A polymerization stress tensometer (PST) is a cantilever-beam based measurement instrument that combines beam deflection mechanics with capacitive sensor technology to measure real-time polymerization shrinkage stress during photocuring of composite resins. Measurement results from a PST can be made traceable to the SI through calibration services offered by NIST.
- **SRI 6008 Ozone Standard Reference Photometer (SRP)**^{12,13}
 The NIST Standard Reference Photometer accurately measures concentrations of ozone (O₃) in air. The measurement principle is based on the Beer-Lambert Law using an internationally accepted absorption cross-section. The SRP is a dual-cell instrument where the charging of each cell alternates between sample and reference sample streams. New SRPs typically agree with SRP 2 (the master SRP maintained at NIST) to better than 0.3 %. The SRP is used by the International Committee for Weights and Measures (CIPM)’s International Bureau of Weights and Measures (BIPM) as the primary standard for numerous national and international ozone-monitoring networks. SRP 0 (a second NIST SRP) is directly compared to the BIPM’s SRP every two years. SRP 0 is then used to transfer the comparison to SRP 2.

1.2. Reference Materials Provided by NIST

NIST currently produces six named types of materials intended to be used as measurement standards: [primary standards \(PSs\)](#), [Standard Reference Materials \(SRMs\)](#), [Research Gas Mixtures \(RGMs\)](#), [NIST Traceable Reference Materials \(NTRMs\)](#), [reference materials \(RMs\)](#), and [Research-Grade Test Materials \(RGTMs\)](#). These standards are all “reference materials” under the BIPM’s International Vocabulary of Metrology (VIM) definition: materials, sufficiently [homogeneous and stable](#) with respect to one or more specified properties, which have been determined by NIST to be fit for their intended use. The RGTMs are a subset of a broader class of “exploratory” materials that NIST uses when investigating new measurement challenges. Not all exploratory materials are intended to be used as – or indeed suited for development to become – any other type of reference material which NIST provides.

Although the acronym “RM” is commonly used for the generic concept “reference material,” in this document “RM” is used only in the context of NIST-provided reference materials. The expanded term “reference material” is used when the generic concept is discussed.

A subset (PSs, SRMs, RGMs, and NTRMs) of the six types of NIST reference materials are certified reference materials (CRMs) under the VIM definition: reference materials, characterized by what NIST considers to be metrologically valid approaches for one or more specified quantitative or nominal

properties, accompanied by documentation that provides the values of the specified properties, their associated statements of confidence, and statements of metrological traceability.

Figure 2 summarizes the relationships among NIST's reference and exploratory materials.

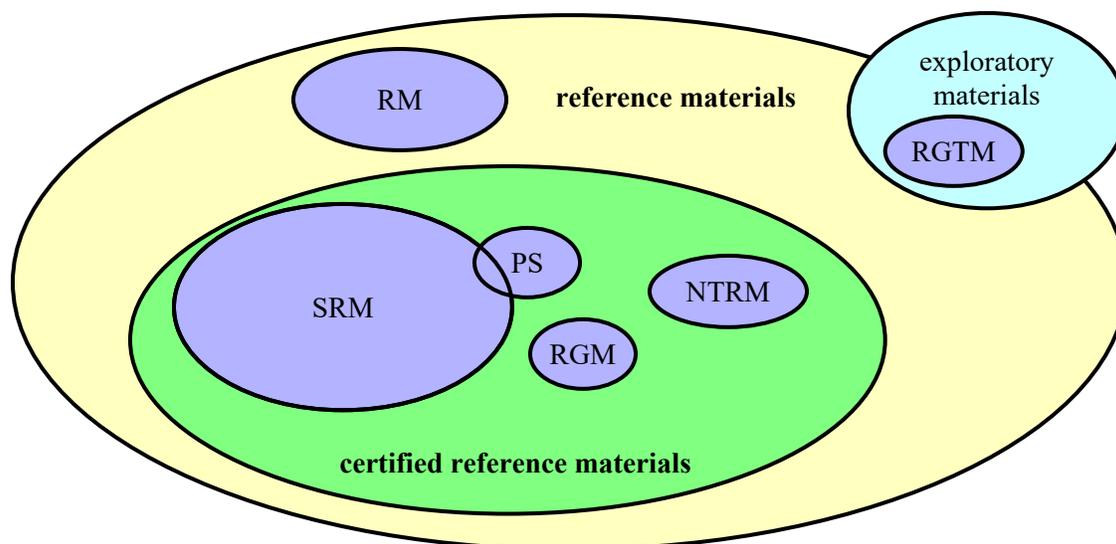


Figure 2. Relationships Among NIST's Reference Materials

The artifact standards identified in the purple ellipses are reference materials (the generic class is indicated by the yellow ellipse) provided by NIST. These materials are all [fit for some specified purpose](#), homogeneous, and stable with respect to one or more specified properties. NIST primary standards (PSs), Standard Reference Materials (SRMs), research gas mixtures (RGMs), and NIST Traceable Reference Materials (NTRMs) are certified reference materials (CRMs, indicated by the green ellipse). These materials deliver [assigned values](#) that are suitable for use in method calibration or validation. Note that some [SRMs](#) are [PSs](#). NIST's Reference Materials (RMs) deliver fit-for-purpose values that are suitable for between-method harmonization and within-method [precision](#) and [stability](#) assessment. Exploratory materials (light blue ellipse) are fit for the purpose of exploring new measurement challenges; Research-Grade Test Materials (RGTM) are exploratory materials that have been shown to be fit-for-purpose homogeneous and stable.

1.2.1. Their intended Purpose(s)

The intended purpose of most NIST CRMs is to provide [higher-order calibration](#) and [validation](#) materials to [secondary standard producers](#) and customers intending to produce [metrologically traceable](#) in-house calibrants and control materials.¹⁴ With few exceptions, NIST does not have resources to fulfill the global demand for reference materials intended for daily use.

While not a change in fundamental policy, this is a change in emphasis. Documents accompanying newly developed reference materials will more explicitly than in the past state the purpose that they are intended to serve.

1.2.2. Certified Versus Non-Certified Values

Certified values delivered by a CRM are believed by NIST to be:

- characteristic of the property(ies) specified ([measurand](#)),
- characteristic of the material at some defined minimum sample size ([homogeneity](#)),
- [stable](#) (for some defined period when properly stored and handled),
- [accurate](#) (unbiased within a specified level-of-confidence interval),
- [metrologically traceable](#) (to a higher-order reference system), and
- documented well enough to provide users with confidence that the certified value is fit for the purpose(s) specified in the documentation supplied to the customer.

These criteria are best thought of as existing along continua from “indisputably inadequate” to “indisputably adequate” where what is “fit-for-purpose adequate” requires decisions informed through good-faith implementation of measurement and quality processes.

NIST certifies a value only when staff believe that all criteria are adequately established. Certification thus explicitly expresses NIST’s considered belief that the certified values are suitable for accurately calibrating or validating [measurement procedures](#), which can then be used to obtain values that are metrologically traceable to a higher-order reference system.

NIST provides CRMs that deliver two generic types of certified values: method-independent and method-dependent. A method-independent value comes from a measurement procedure for which the measurand definition is independent of the procedure used to obtain the value. All certification methods that provide metrological traceability to the SI produce method-independent certified values.

The measurand for method-dependent values is operationally defined by the procedure used to obtain the value. As discussed in Section 3.5, there are (at least) two subtypes of these operationally defined measurands: those for which the method is the highest-order reference system (e.g., pH and Rockwell Hardness Scales) and those that measure a constituent or property that is a proxy for a more difficult to measure constituent or property (e.g., Kjeldahl total nitrogen used to estimate total protein¹⁵).

NIST will not provide any value when NIST staff believe that one or more of the first three of the above criteria (measurand, homogeneity, and stability) are not adequately established. NIST provides non-certified values only when the first three are believed to be adequately established, but one or more of the following three (accuracy, traceability, and documentation) are not.

1.2.3. Reference, Information, and Indicative Values

From 1987 to the publication of this document, NIST non-certified values were called “NIST Reference Values” if an (incomplete) uncertainty estimate was associated with the value. Values without any associated uncertainty were called “NIST Information Values.”¹ Some reference materials from other providers describe non-certified information as “indicative values.” NIST does not use this term.

1.2.4. Documenting Certified Values

Since NIST asserts that a certified value provides an estimate of the [true value](#) of a defined measurand, the documentation provided to the customer clearly differentiates values for method-independent measurands from values for operationally defined measurands. When a certified value has a measurand that is method-independent, the documentation provided to the customer defines the measurand but needs not provide details of the measurement procedure(s): any valid method that is working properly should return the true value. When a certified value is operationally defined, the documentation defines the measurand and, at minimum, references publicly accessible literature that describes the procedure.

Using any value for its intended purpose requires that customers know how confidence in the value was established. For quantitative values, confidence is expressed as an interval that contains the true value with a stated [level of confidence](#), typically 95 %. For nominal values such as measurand [identity](#), the documentation briefly describes the criteria used to establish confidence. Only nominal values that have been established with “High Confidence” can be certified.

Some users of a NIST CRMs may need access to details of the certification to use a certified value for their own purposes. The experimental details, data, and data evaluation techniques are made publicly available in a NIST SP 260-series Special Publication, a peer-reviewed article, within the documentation that accompanies the material (e.g., the Certificate of Analysis), or some combination thereof.

1.2.5. Documenting Non-Certified Values

Ironically, non-certified values require that the documentation supplied to the customer provides a much more complete description of the value and its associated confidence than do certified values. To be useful to a customer, the documentation includes:

- The measurement procedure(s) used, in enough detail for an informed customer to understand it, as appropriate for the NIST-intended use.
- What the value represents; e.g., the mean of samplings from one unit of material, the grand mean of results from multiple units of the material, or the median of an [interlaboratory study](#) (ILS).
- What the associated uncertainty or confidence statement represents; e.g., technical precision, repeatability and homogeneity, or reproducibility as estimated from an ILS.

The documentation must not imply that NIST asserts that a non-certified value represents the true value of the measurand. In the documentation that accompanies the material, non-certified values are separated from certified values.

1.2.6. Other Forms of Data

When there are values of potential interest to users that cannot be associated with estimates of uncertainty or indications of confidence, these values can be included within NIST CRM documents as part of textual descriptions or in bulleted lists clearly associated with descriptive text. Examples of such data include instrument settings, model parameters, limits of detection, and approximations.

In addition to values, some NIST CRM documents include data such as images and plots considered to be useful to customers. Enough information is provided within the documentation to enable these data to be reproduced. .

1.2.7. Primary Standards (PSs)

NIST primary standards (PSs) are suitably characterized materials whose purity values and associated uncertainties are [fit-for-purpose](#). The values assigned to PSs are metrologically traceable to internationally recognized higher-order reference systems, typically the SI. The values assigned to PSs are described in NIST internal documentation.

Most materials intended for use as PSs are acquired in small quantities, characterized, and then used to calibrate and to provide metrological traceability to measurement results of other NIST-provided measurement tools. Most PSs are not available to customers, although some may be shared with [collaborating measurement organizations](#) and [secondary standards producers](#) in support of national and international measurement comparability. A few materials, mostly for measurands of clinical relevance such as glucose¹⁶ and cholesterol¹⁷, are purchased in quantity and characterized for use as PSs that are available for purchase as SRMs.

1.2.8. Standard Reference Materials® (SRMs®)

Standard Reference Materials (SRMs) are CRMs that deliver values certified by NIST. All SRMs deliver at least one certified property value that is:

- metrologically traceable to an internationally recognized higher-order reference system, such as the SI, and
- deemed by NIST to be suitable for providing unbiased calibration and/or validation of measurement procedures.

SRMs may also deliver non-certified information. The certified and non-certified values are described in separate sections within the SRM's documentation: "Certificate" for physical or engineering performance properties and "Certificate of Analysis" for specific chemical properties.

SRMs are issued as "SRM x" where "x" is typically a series of digits from 1 to 5999, with an alphabetic or lot number suffix indicating re-issues.

Note: "Standard Reference Material" and "SRM" are trademarks registered to NIST by the United States Patent and Trademark Office.

1.2.9. Research Gas Mixtures (RGMs)

Research gas mixtures (RGMs) are specialty gas CRMs produced as single units in collaboration with an industrial or government agency partner. RGMs are certified using the same protocols used for batch-certified NIST gas SRMs. RGMs are identified using the cylinder's identification code. The certified values are described in a "Certificate of Traceability."

1.2.10. NIST Traceable Reference Materials^{CM} (NTRMs^{CM})

NIST Traceable Reference Materials (NTRMs) are CRMs that are certified by NIST in collaboration with a secondary standards producer, with a well-defined metrological traceability linkage to existing SRMs or PSs. This linkage is established via criteria and protocols defined by NIST to meet the needs of the community served. Reference materials producers adhering to these requirements can use the "NTRM" Certification Mark (CM). The certified values are described in a "Certificate of Traceability." Two NTRM programs have been established: an ongoing specialty gas program^{18,19} and a spectrophotometric filter program²⁰ that ended in 2005.

1.2.11. Reference Materials (RMs)

NIST's reference materials (RMs) deliver property values for established measurands that are fit for the materials' intended uses, including between-method harmonization, within-method precision assessment, and process stability assessment. RMs are issued as "RM 8xxx," where the "xxx" is a unique series of three digits. These materials and values have historically been described in a "Report of Investigation" rather than a Certificate or Certificate of Analysis. For RMs developed after the publication of this document, these documents will be termed "Reference Material Information Sheets."

1.2.12. Research-Grade Test Materials (RGTMs) and Other Exploratory Materials

NIST's Research-Grade Test Materials (RGTMs) are a subset of the "exploratory materials" that NIST investigates for use in studying new measurement challenges. RGTMs are issued as "RGTM 1xxxx" where "xxxx" is a unique series of four digits. RGTMs are often first used as test materials in a NIST-sponsored ILS. They are prepared to be [fit-for-purpose](#) homogeneous and stable but typically have not been quantitatively evaluated for all properties of potential interest. Given enough community interest and suitable funding, results from the study of RGTMs may lead to development of higher-order reference materials.

Other exploratory materials obtained during the very early stages of an investigation or for use as samples in a single ILS may be useful without meeting the homogeneity and stability requirements for consideration as a reference material. RGTM differ from other exploratory materials primarily in the amount of material purchased and the characterization effort expended prior to their first use.

1.3. Stages in the Reference Material Project Development Process

Figure 3 displays the typical stages and decision points in RGTM, RM, and SRM development.

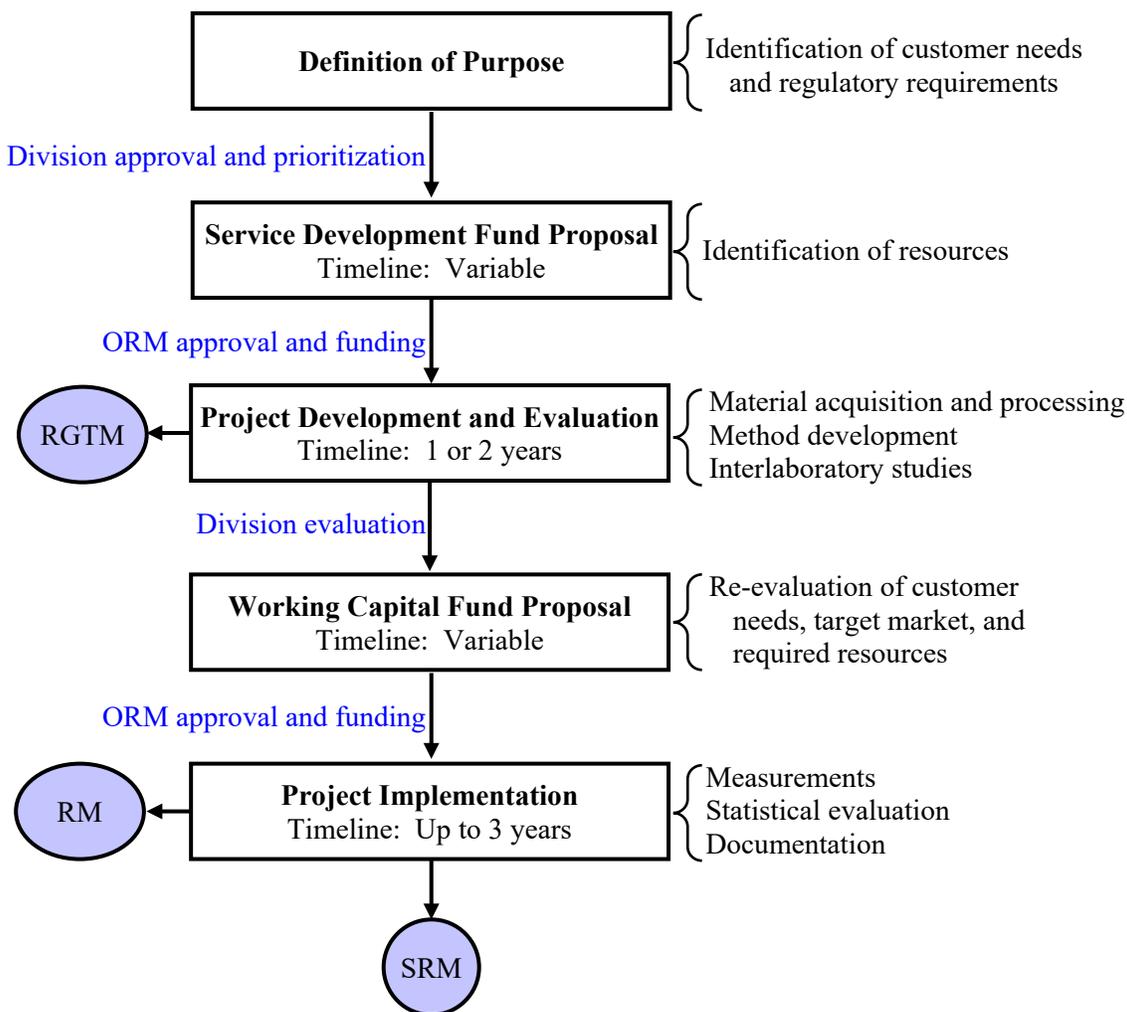


Figure 3. Steps in Reference Material Development

Materials acquired for evaluation and procedure development may become Research-Grade Test Materials (RGTM). Depending on the purpose of the project, the results from the material evaluations, and availability of resources, some RGTM may become NIST Reference Materials (RMs) rather than Standard Reference Materials (SRMs) or may be used for other purposes, such as interlaboratory study samples. The NIST Office of Reference Materials (ORM) funds the development of most SRMs through a cost-recovery program. Service Development Fund and Working Capital Fund proposals are typically evaluated annually, but occasionally on demand or by request. Note: “Division” as used here is NIST’s designation of the management organization responsible for providing the required measurement services.

2. Definitions and Explanations

There are numerous sources of metrological terminology. NIST recognizes the third edition of the International Vocabulary of Metrology (VIM), JCGM 200:2012 *International vocabulary of metrology – Basic and general concepts and associated terms* (VIM3)⁴, ISO Guide 30:2015 *Reference materials – Selected terms and definitions*⁵, and ISO International Standard 17034 *General requirements for reference material producers*³ as authoritative sources. These documents are referenced below as [VIM3:section], [ISO Guide 30:2015:section], and [ISO 17034:2016:section].

NIST aims to remain generally consistent with national and international documentary guides, including the International Union of Pure and Applied Chemistry (IUPAC)'s "Gold"²¹ and "Green"²² Books and the International Union of Pure and Applied Physics (IUPAP)'s "Red Book"²³, but reserves the right to define and use metrological terminology in ways that it deems best, that are consistent with NIST's mission, and that serve U.S. national needs. NIST disseminates such definitions and usage in documents such as this one, and in other NIST publications and documents supporting the NIST Quality Management System.⁶

Note: Metrological terminology, like all living vocabularies, evolves over time. NIST's trademarked "Standard Reference Material" and its acronym "SRM" evolved from the descriptive term "Standard for...", used at the founding of the original organization (Bureau of Standards) to the name "Standard Sample" used until 1967 by NIST's predecessor organization (National Bureau of Standards). As other organizations began to produce similar tools, the international community adopted "certified reference material" (CRM) as the general term. To preserve the NIST brand (and because the term is written into U.S. federal legislation), with the exception of the Research Gas Mixtures (RGMs) and NIST Traceable Reference Materials (NTRMs), NIST-certified CRMs will continue to have the name Standard Reference Material (SRM).

2.1. Accuracy

Measurement accuracy is metrologically defined as "closeness of agreement between a measured quantity value and a true quantity value of a measurand" [VIM3:2.13]. When used to characterize replicate results of a chemical measurement procedure, accuracy is a qualitative term that combines the quantitative concepts of precision and trueness.²¹ Measurement precision characterizes the closeness of agreement of replicate results with each other. Measurement trueness (absence of bias) characterizes the closeness of the mean of the replicates to the true value. Figure 4 displays the interrelationships among the concepts.

When applied to a single measurement value (i.e., one of the red dots in Figure 4), "accuracy" is the same as trueness since there are no replicates to compare. This is related to the common (in non-metrological circles) "accuracy and precision" characterization. However, this usage complicates discussion of "measurement accuracy" until all parties share an understanding of the various concepts.

Although the replication is not explicit, a measurement result expressed as a value and an associated standard uncertainty, x and $u(x)$, can be regarded as summarizing replicate results from a measurement procedure. The x estimates the true value and $u(x)$ expresses and summarizes contributions from all recognized and evaluated sources of uncertainty, including potential bias and lack of repeatability or reproducibility.

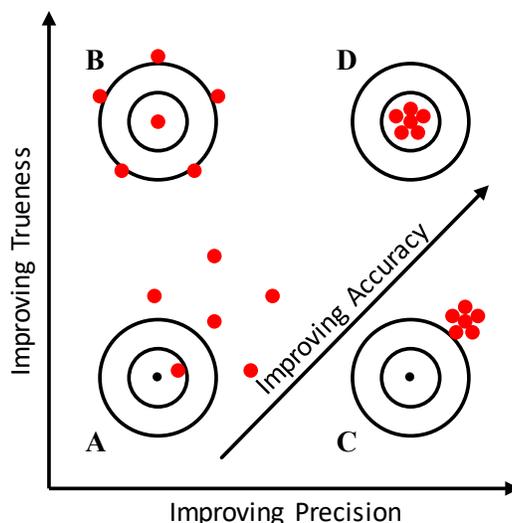


Figure 4. Relationships Between Measurement Accuracy, Precision, and Trueness

The red dots represent individual measurements. The center dot in each target represents the ideal or “true” value for a measurement procedure, where the procedures are: A) imprecise and biased; B) imprecise and true; C) precise and biased; and D) precise and true. Figure adapted from [24].

2.1.1. Precision

Measurement precision is metrologically defined as “closeness of agreement between ... measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions” [VIM3:2.15]. That is, precision characterizes how well specified types of replicate results agree. Precision improves as the replicate results become closer together (i.e., as the standard deviation decreases), where “closer” can be expressed numerically as the standard deviation of the replicates.

The description of precision depends on the conditions under which the measurements were made.²⁵ The most stable condition resulting in the least variability, sometimes called “instrumental” or “technical” precision, characterizes replicate determinations of one fully prepared sample made in the same session. “Repeatability” conditions characterize replicates of independently prepared test portions that are prepared by the same analyst using the same materials and equipment over a relatively short period of time. “Reproducibility” conditions characterize replicate results for samples prepared independently by different analysts, in different laboratories using different materials, instruments, and potentially measurement procedures over a relatively long period of time. Conditions more complex than repeatability but less complex than reproducibility are termed “intermediate” with the specific conditions described; e.g., “long-term, within-laboratory, same equipment, different analyst intermediate precision.” As shown in Figure 5, imprecision is expected to increase as the conditions become more complex.

While reproducibility precision provides the most realistic estimate of measurement variability, long-term between-analyst intermediate precision is often the most practically realizable estimate that can be achieved without evaluating a material in an ILS.

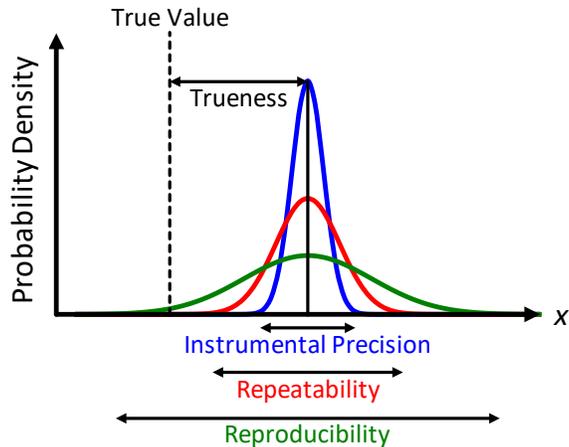


Figure 5. Probability Densities for Precision Conditions at Fixed Trueness

The tall, narrow blue curve represents instrumental precision, the middle red curve represents precision expected for measurements made under repeatability conditions, and the broad green curve represents precision expected for measurements made under reproducibility conditions. The vertical dotted line indicates the true value of the measurand; the horizontal arrow connecting the center of the curves and the true value represents the measurement trueness. The arrows below the horizontal axis span the central 95 % of the area underneath each curve.

2.1.2. Trueness

Measurement “trueness” is metrologically defined as “closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value [VIM3:2.14]. Trueness can be colloquially expressed as “lack of bias,” characterizing the closeness of agreement between the mean of replicate values and a higher-order reference or “true value.” Trueness can be quantified as the difference between the mean and the true value, with trueness improving as the difference becomes smaller. It is often more convenient to speak of bias increasing/decreasing as the difference increases/decreases.

2.1.3. True Value

The true value of a quantity or quality is the value that a measurement unaffected by measurement error would produce. While exact knowledge is beyond human reach, the goal of all the modes used to certify SRMs is to establish the true within some specified uncertainty, with stated confidence.

2.1.4. Detection and Quantification Limits

Measurands that are determined to be present in a material at no more than some limiting value can be specified as a range. Measurands that cannot be conclusively detected can be stated as less-than-or-equal to the detection limit, $x \leq L_D$.²⁶ Measurands that are detected but not reliably quantified can be specified at concentrations greater than the detection limit but less than or equal to the quantification limit, $L_D < x \leq L_Q$.²⁶ The value of a limit need not be associated with a further confidence statement. Any uncertainty in determining a limit should be addressed by expanding the stated range.

A range may be a certified or a non-certified value depending on how thoroughly it has been characterized.

2.2. Collaborators

ISO Guide 30:2015 equates “collaborator” with “subcontractor,” which is defined as “body (person, 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] on behalf of the [reference material] producer, on a contractual basis, either paid or non-paid” [adapted from ISO Guide 30:2015:4.6]. However, this document restricts the term to apply only to organizations or individuals who help characterize NIST materials. This document recognizes three types of collaboration based on the level of engagement with NIST.

2.2.1. International Peer Organizations

Measurements made by many national metrology institutes (NMIs) and designated institutes (DIs) may have formal equivalency with those made by NIST through the CIPM Mutual Recognition Arrangement (MRA).²⁷ While DIs typically have more limited responsibilities than do NMIs, NMIs and DIs are both at the top of their national calibration hierarchies for defined types of measurements. These organizations typically interact with NIST through comparison studies authorized by the CIPM and conducted by the Consultative Committee responsible for the relevant metrology area. The Consultative Committee for Mass and Related Quantities (CCM) is responsible for supporting comparisons involving hardness measurements. The Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM) is responsible for supporting comparisons involving chemical and biological measurands.

2.2.2. Expert Collaborators

In this document, the unofficial term “expert collaborator” is used for organizations other than NMIs and DIs that engage with NIST through direct comparison of measurement capabilities through bilateral or small multi-center studies designed to address specific issues. The organizations include:

- United States governmental agencies such as the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), National Center for Atmospheric Research (NCAR), U.S. Geological Survey (USGS), and U.S. Department of Agriculture (USDA).
- International agencies such as the International Bureau of Weights and Measures (BIPM), International Atomic Energy Agency (IAEA), World Anti-Doping Agency (WADA), and World Meteorological Organization (WMO).
- Standards development organizations that validate the standard test procedures, practices, and guides they produce. Examples include the standard test development committees of AOAC International, ASTM International, and the Clinical & Laboratory Standards Institute (CLSI).
- Individuals and organizations in academia, government, and the private sector that have the needed capabilities, are willing to contribute their efforts, and are willing to perform experiments in a way that satisfies the NIST Quality Management System.

2.2.3. Participants in Interlaboratory Studies

Consensus results from ILSs are a valuable and increasingly important source of data used to help NIST characterize materials. While the participants in such studies are collaborators, they need not be measurement experts if there are enough participants in the study to provide reliable consensus estimates. What is considered “enough” depends on how different the results are, the data analysis methods used, and whether the ILS included control materials.

2.3. Fitness for Purpose

“Fitness for purpose” is a vital metrological concept, but it is not formally defined. Rather, it addresses the straightforward question “Does this instrument or procedure or material adequately meet the requirements of the purpose for which it is to be used?”

Fitness is necessarily a relative concept, because what is fit for one purpose may be unfit for even closely related purposes. For example, an SRM designed to support the measurement of chromium in a sediment using procedures that consume 500 mg samples may not be sufficiently homogeneous to support microanalysis methods that are limited to no more than 5 mg. What was fit for purpose yesterday may not be fit for the identical purpose tomorrow, if regulatory action limits are changed.

In general, the intended purpose of NIST’s SRMs is to provide higher-order calibration and validation materials to secondary standard producers and customers intending to produce metrologically traceable in-house calibrants and control materials. NIST’s SRMs are fit for their intended purpose if they deliver to the intended customers “true enough” values for useful levels of the desired measurands in a timely manner and at reasonable cost. SRMs that are not adequately fit for customer purpose(s) are not useful even when all design criteria are satisfied. It is therefore imperative that new and renewal SRMs be designed relative to the needs and capabilities of properly targeted customers. It is a waste of effort and resources to produce a material that is “better” – and consequently more expensive to certify and to sell – than what the customer requires.

2.4. Interlaboratory Study (ILS)

For use with the “Certification Modes” described in Section 3, an ILS is any collaborative study of a NIST material that provides enough technically valid measurement results to enable generation of a consensus value whose associated uncertainty is fit for purpose. Such a consensus value and uncertainty may then be used to help certify values without NIST having specific knowledge of the participants’ measurement processes. NIST need be neither the coordinator nor a participant of an ILS to use the reported information.

When the ILS yields fewer than five technically valid results, NIST must have enough information about the methods and calibrants used to achieve those results so that a summary report can be prepared that satisfies the NIST Quality Management System. The collaborators do not need to provide formal written reports as long as NIST receives the needed information.

2.5. Higher-Order

Another important concept that is not formally defined, “higher-order” is used often in metrological contexts, including reference materials, measurement procedures, measurement results, and reference systems. The term usually indicates that whatever the compound adjective modifies is “among the best” (or “the best”) currently available within a given hierarchy. For example:

- **Higher-order metrological traceability**
Traceability to the top link in an [unbroken chain of comparisons](#), typically to the SI.
- **Higher-order materials**
Materials that provide higher-order metrological traceability when used as calibrants. PSs are higher-order CRMs while CRMs are higher-order reference materials.
- **Higher-order reference measurement procedures**
RMPs that provide accurate results traceable to a higher-order reference system through a minimal number of linkages. Coulometric titrimetry, gravimetry, isotope-dilution mass-spectrometry (ID-MS), and quantitative nuclear magnetic resonance (qNMR) are examples of higher-order RMPs that do not require calibration with a calibrant of the same kind as the

sample. However, many analytical procedures can be of higher-order simply by calibrating with a higher-order calibrant of the same kind as the sample.

- **Higher-order measurement results**

Results produced using higher-order procedures, validated by comparison to measurements made on higher-order reference materials. Certified values are higher-order results.

- **Higher-order reference systems**

Traditionally, NIST certified values have exclusively been metrologically traceable to the SI. However, there are internationally recognized material- and procedure-based reference systems for measurands where traceability to the SI is impractical or irrelevant. Examples include the World Health Organization's materials that define international units of biologic activity, Cereals and Grains Association Method 32-45.01 procedure for dietary fiber, and DNA sequencing for establishing biological identity.

2.6. Homogeneity and Stability

To be useful, any PS, SRM, RGM, NTRM, RM, or RGTM must be fit-for-purpose homogeneous and stable for the period of validity. However, homogeneity (uniformity of composition within a material) and stability (uniformity of composition over time) are relative, not absolute, concepts.

2.6.1. Homogeneity

Homogeneity is metrologically defined as “uniformity of a specified property value throughout a defined portion of a reference material” [ISO Guide 30:2015:2.12]. [ISO 17034:2016:7.10] describes requirements for assessing the homogeneity of reference material constituents. An analyte dispersed in a granular material may appear to be uniformly dispersed if suitably large samples are analyzed but may be quite heterogeneous (as a result of “nuggets,” individual granules enriched in one or more analytes)²⁸ when smaller sample sizes are used. At any given sample size, the uniform dispersal of one analyte does not necessarily indicate the material is suitably homogeneous for other analytes, especially those that do not have similar physicochemical properties. Materials that are suitably homogeneous for relatively imprecise measurement procedures may not be so for more precise procedures.

Homogeneity is not just an issue for solids; gases and liquids can stratify within their containers.

However, assessing the homogeneity of a solid reference material generally requires more complex procedures that depend on the form of the material: e.g., disk, rod, chip, granule, or powder.

For all reference material forms, it is critical that the intended purpose for the material is well-defined and the material is prepared for that purpose. The development process must define the storage conditions, handling practices, mixing and sampling practices, and minimum sample size that will satisfy the purpose of the reference material.

2.6.2. Stability

Stability is metrologically defined as “characteristic of a reference material, when stored under specified conditions, to maintain a specified property value within specified limits for a specified period of time” [ISO Guide 30:2015:2.15]. There are two major aspects to stability for NIST-issued reference materials: 1) while stored at NIST and under our control and 2) during shipment.

2.6.2.1. Transportation Stability

Transportation stability, often referred to as “short-term stability,” is “stability of a reference material property for the time period and conditions encountered in transportation to the user of the reference material” [ISO Guide 30:2015:2.16]. ISO Standard 17034 requires producers to “assess, by experimentation if necessary, the stability of all relevant properties of [a reference material] under proposed conditions of transport, and choose transport conditions to maintain stability during transport” [ISO 17034:2016:7.11].

While NIST’s packaging and shipping processes are intended to minimize the opportunity for such changes, the stability of materials thought to be prone to degradation should be evaluated under realistic conditions (e.g., vibration, temperature, freeze-thaw cycles). If degradation is found likely, special handling instructions may be required and an additional component of uncertainty included in the uncertainty budget for any affected property value to account for potential degradation during shipment.

2.6.2.2. Storage Stability

Often referred to as “long-term stability,” storage stability is “stability of a reference material property over an extended period of time” [ISO Guide 30:2015:2.17]. ISO Standard 17034 requires producers to “assess, by experimentation if necessary, the stability of all relevant properties of [a reference material] under proposed storage conditions and choose pre-treatment, packaging and storage conditions in accordance with the results of the assessment” [ISO 17034:2016:7.11]. An important step in evaluating the uncertainty of an assigned property value is to consider including a component of uncertainty to account for potential degradation during long-term storage.

For many inorganic analytes, the amount of substance content in matrices such as metals and ores is unlikely to change much over even long time periods regardless of handling and storage conditions. For some inorganic analytes in solution and many organic analytes in any matrix, the contents can change rapidly, even when materials are carefully handled and stored. Analytes in mixtures can react with each other, their matrices, or their packaging, causing the amount of substance to decrease or increase over time.

Compositional changes that are fit for a single, quickly completed ILS may not be fit for materials that will be stored for years before sale.

It is impractical to experimentally measure the compositional stability of every constituent of interest in even a single complex material on a regular basis. NIST therefore monitors its products during their period of validity and, if substantive technical changes occur that affect the values, takes corrective action and notifies the users and purchasers. The following are examples of monitoring techniques that help make sure that NIST is aware of changes during the lifetime of the product:

- **Scheduled evaluation against primary standards** of selected constituents, typically in relatively novel materials.
- **Evaluation through use of materials as controls** during the development of a reissue or new reference material of similar matrix. For example, Figure 6 displays results of NIST measurements made during the past 19 years for selected elements in SRM 1566b Oyster Tissue. While the analytical quality of individual values may differ, collectively they can provide reliable evidence that at least most of these analytes are stable in complex organic matrices over long periods of time.
- **Evaluation through use of materials as ILS controls and/or unknown samples.** Figure 7 displays consensus values for total β -carotene in the component sera of four reissues of SRM 968 Fat-Soluble Vitamins in Human Serum. Distributing the same materials in multiple studies of similar nature directly addresses stability not only in the materials themselves and the distribution processes but also in future materials of similar matrix.

- **Scientific judgment** about the expected behavior of constituents in similar materials informed by experience with similar measurands. Since short-term studies established that *trans*- β -carotene is a reasonable proxy for other fat-soluble vitamin-related analytes in serum,²⁹ the long-term stability evidence provided in Figure 7 is believed to extend to the other carotenoids in these same sera.
- **Continuous interaction with customers and rapid responses to inquiries.** As part of NIST’s Quality Management System,⁶ customer inquiries and comments are addressed promptly and thoroughly. Complaints trigger a review of available data and, if the potential deficiency is found credible, action is taken to identify its cause, develop a remedy, and determine if any other product is affected.

When the validity of a certified value becomes suspect, the material is put “on restriction” and sales are ceased until the issue is resolved by direct experimental measurements.

Note: While NIST’s customers sometimes incorrectly attribute issues with their measurement procedures to issues with the materials, they also sometimes fail to recognize that a discordance may indicate a real problem with the material or its certificate;³⁰ therefore inquiries are always welcomed.

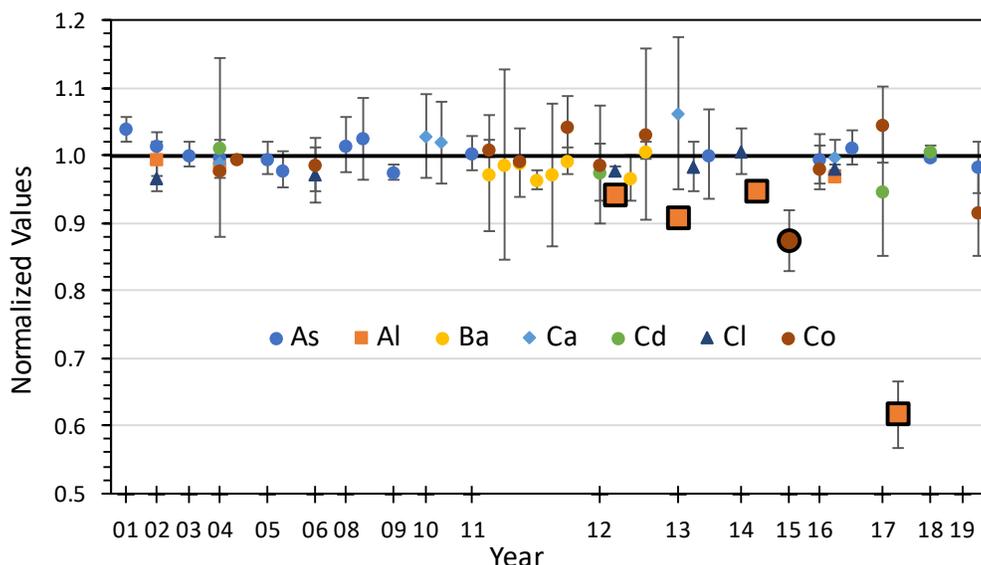


Figure 6. Stability of Selected Elements in SRM 1566b Oyster Tissue

Each symbol represents a NIST measurement, $x \pm u(x)$, of SRM 1566b used as a control to help validate measurements of another material. All data are normalized to the analyte’s certified value. The large symbols with the black border (four Al and one Co) denote results that do not adequately agree with the certified value. Based on the erratic pattern of the excursions over time and the absence of correlated excursions between elements with similar properties, the excursions likely represent measurement rather than material stability issues. Figure courtesy of Savelas A. Rabb, NIST.

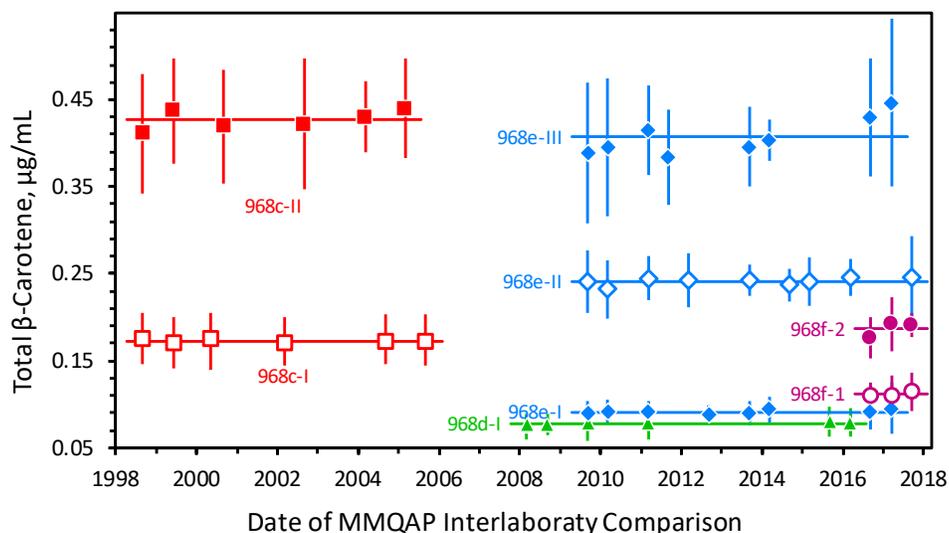


Figure 7. Stability of Total β -Carotene in Frozen Human Serum

Each symbol represents the consensus ILS result, $x \pm u(x)$, for total β -carotene in one serum of the SRM 968 Fat-Soluble Vitamins in Frozen Human Serum series. The horizontal lines represent the mean of the individual results. These materials were distributed as unknowns in the NIST-coordinated Micronutrients Measurement Quality Assurance Program (MMQAP).¹⁰³

2.6.3. Period of Validity

A period of validity is the time during which certified values are expected to remain correct within the stated uncertainty. NIST makes reasonable efforts to verify the [stability](#) of the material and its constituents and properties. For most materials, the period of validity will be a specific number of years, estimated from stability testing and experience with similar [measurands](#). For some materials, such as metals and most alloys, the period of validity may be indefinite, based on scientific knowledge about the materials. In all cases, due diligence is required to justify the designation and to provide instructions for storage, handling, and use that can be expected to help maintain stability. Periods of validity may be extended based on verification of material stability.

2.6.4. Expiration Date

Unless the period of validity is indefinite, the documentation provided with each reference material states an expiration date after which the assigned values are not supported. The expiration date is based on the established period of validity.

Most NIST SRMs and RMs are put on restriction (i.e., sales are ceased) three months prior to the expiration date; gases are restricted one year prior to their expiration date. (These restrictions are for purposes of internal stock control; they do not affect the period of validity.) If the amount of stock, customer needs, and availability of staff and instrumentation justify the effort, resources are devoted to determining whether the period of validity can be extended. If there is adequate evidence of [stability](#), the expiration date stated in the documentation is updated.

Note: Customers are not notified of an extended expiration date. It is up to the customer to check that their documentation is current. This can be accomplished by contacting the SRM Program: telephone (301) 975-2200; fax (301) 948-3730; e-mail srminfo@nist.gov; or via the Internet at <https://www.nist.gov/srm>.

2.6.5. Revision History

The documentation (i.e., Certificate of Analysis, Reference Material Information Sheet, etc.) for NIST's reference materials may undergo revision during the period of validity. Changes include editorial revision, extension of the period of validity, upgrading non-certified values to certified status, downgrading certified values to non-certified status, and removing values. A revision history is provided, typically on the document's last page.

2.7. Material Handling and Storage

Tracking and ensuring the integrity of materials and data throughout a reference material development process is fundamental to successfully delivering values that are fit for their intended purposes. [ISO 17034:2016:7.4] specifies requirements for all materials. ISO 20387:2018 *Biotechnology — Biobanking — General requirements for biobanking*³¹ specifies requirements for biological materials.

2.8. Measurand

A measurand is the quantitative or qualitative property that is the object of measurement. The [VIM3:2.3] defines a quantitative measurand as the “quantity intended to be measured”, and supplements this definition with these Notes, which also apply to qualitative measurands, with obvious modifications:

- specifying a measurand requires knowledge of the kind of quantity, description of the substance carrying the quantity, relevant components of the substance, and the chemical entities involved.
- while sometimes used as a synonym, “analyte” refers to a chemical entity not a quantity.

The distinction between analyte and measurand is discussed at length in reference³², along with the logic behind the current definition's evolution from the “quantity subject to measurement” definition given in the second edition of the VIM (VIM2).³³

Note: The measurand is not necessarily what is measured. For instance, measurement of the analyte total nitrogen using the Kjeldahl method¹⁵ is traditionally used to value assign the measurand total protein content of many foods.

It is critical that the measurand be (fit-for-purpose) completely specified for a value to be considered certifiable. Most chemical measurands are specified as the type of quantity (e.g., mass fraction expressed as mg/g, mass concentration expressed as $\mu\text{g/mL}$, pH) of the target analyte (e.g., iron, total retinol, conventional activity of the hydronium ion) in a matrix (e.g., nitric acid at an amount of substance concentration of about 1.6 mol/L, normal human serum, aqueous solution prepared from solids according to a specific protocol.) Describing a value as the “mass fraction of hexavalent chromium in aqueous industrial effluent evaluated using EPA Method 7196A” is much less open to misinterpretation than is “concentration of chromium in water.”

2.8.1. Nominal and Ordinal Properties

Nominal and ordinal properties are qualitative properties, often called “categorical properties”³⁴ when taken together because their values are names of categories, or classes, whose elements have particular values of defining properties in common (the defining properties may be qualitative or quantitative). Being a rare-earth or an alkali metal is a nominal property of the chemical elements. Determining whether a compound includes a rare-earth may involve both quantitative and qualitative measurements. Being acidic is a property of an aqueous solution, which may be determined using a pH indicator.

The values of ordinal properties can be ranked (ordered from smallest to largest) yet they are not quantitative — of them it can be said only whether one is more or less than another, but not by how much. Blue litmus³⁵ paper will turn red when dipped in an acidic solution, and will remain blue in an alkaline solution, thus indicating only that the pH of the former is lower than the pH of the latter. Even when the

values of ordinal properties are expressed numerically, as they are in the Mohs hardness scale³⁶ for minerals, the numbers serve only to indicate rank order, being otherwise unsuitable for including in arithmetic operations.

NIST's understanding of "measurement" includes value-assignment to qualitative or quantitative properties.³⁷ Both VIM3 and ISO Guide 30:2015 recognize that nominal properties are measurands that can be value-assigned using the same concepts as traditional, quantitative measurands, and whose associated uncertainties may be expressed quantitatively:

- "‘uncertainty’ covers both ‘measurement uncertainty’ and ‘uncertainty associated with the value of a nominal property,’ such as for identity and sequence. ‘Traceability’ covers both ‘metrological traceability of a quantity value’ and ‘traceability of a nominal property value’ [VIM3:5.14 Note 2].
- "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" [ISO Guide 30:2015:2.2 Note 1].

Since at least 1964, NIST has provided CRMs that deliver nominal properties. Standard Sample 2106 ISCC-NBS Centroid Color Charts³⁸, a collection of 251 paint-on-paper samples, illustrated a set of standard colors. SRM 1810 Linerboard Standard for Tape Adhesion Testing³⁹ delivers a surface that adhesive tape either does or does not stick to under defined conditions. SRM 1196a Standard Cigarette for Ignition Resistance Testing⁴⁰ delivers cigarettes that either do or do not extinguish before burning their whole length. These and related properties are typically metrologically traceable to specified scales or test methods.

2.8.2. Identity

The identity of a chemical element or compound, rock or mineral species, or living organism, is a nominal property. NIST recognizes that identity is a nominal property that can be delivered by reference materials, and that the associated uncertainty can be expressed either quantitatively, or in an ordinal scale.^{41,42} For example, SRM 3246¹²⁹ assigns the species value *Ginkgo biloba* to the material, based on identifying sequences of nucleotides in its DNA, and expresses the associated uncertainty qualitatively, in an ordinal scale that represents the strength of the belief in the assigned value.

Chemical identity may be regarded as being metrologically traceable to the geometric-distance matrix⁴³ (three-dimensional structure) of a compound. Biological identity can be regarded as being traceable to characteristic DNA or amino acid sequences of the holotype (type specimen) of the organism, available in internationally recognized databases. The requirements for adequately documenting traceability to these standards are critically dependent on the needs and agreement of the relevant measurement communities.

2.9. Measurement Method, Procedure, and Process

While it is common practice to describe specific and detailed measurement protocols as “test methods,” a measurement *method* is officially a “generic description of a logical organization of operations used in a measurement” [VIM3:2.5]. A measurement *procedure* is a “detailed description of a measurement according to one or more measurement principles and to a given measurement method, based on a measurement model and including any calculation to obtain a measurement result” [VIM3:2.6].

This document uses the term *process* to encompass how analytical information from multiple measurement procedures and studies is combined to produce measurement results. Such processes typically involve several pre-analytical steps (e.g., sampling, storage, transport) required to obtain a characteristic subsample of a test material; pre-instrumental steps (e.g., extraction, chemical modifications, dilution, preparation of aliquots of the subsample and validation materials) to convert the aliquots to forms suitable for analysis with one or more measurement procedures; calibration; measurement of sample and validation aliquots, including homogeneity and stability studies; interpretation of the data; and calculation of the measurement result. Figure 8 outlines the generic steps, and the typical flow of information between the steps, for processes that are intended to produce certified values.

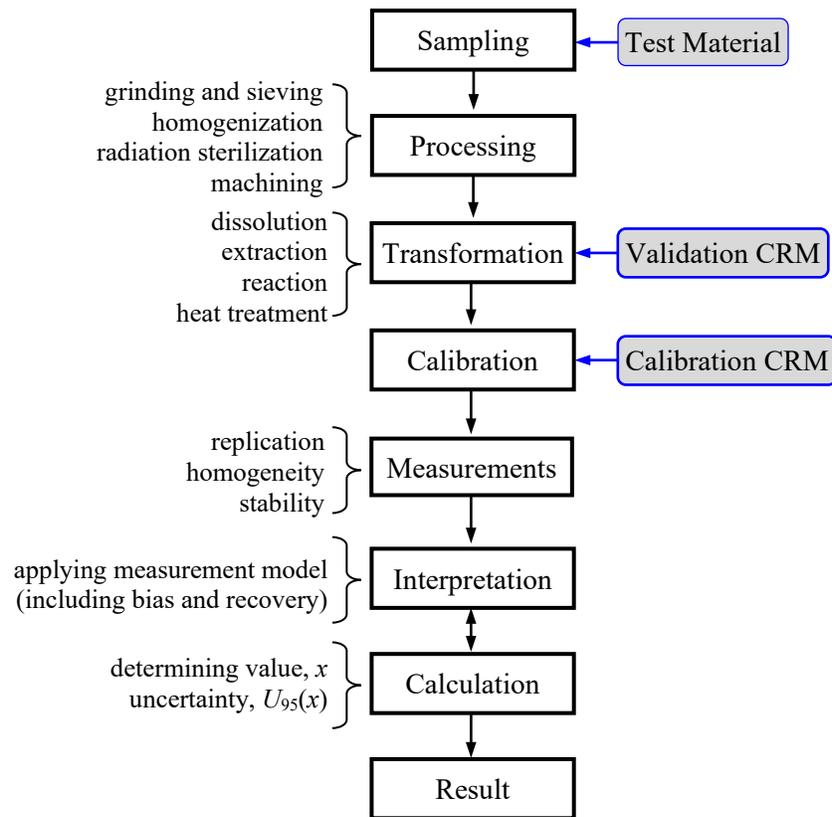


Figure 8. Steps in a Generic Measurement Process for Certifying Values

The grey shapes to the right indicate the step at which the test material, validation CRMs, and calibration CRMs enter the process. The entries to the left are examples of activities associated with the respective stages of the process. The arrows that connect the steps represent transfer and often storage of materials and data. In practice, interpretation and calculation often proceed iteratively.

2.9.1. Method Calibration

Calibration is formally defined as an “operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication” [VIM3:2.39], where indication is defined as a “quantity value provided by a measuring instrument or a measuring system” [VIM3:4.1]. That is, calibration provides the means for translating instrumental indications (readings) into measured quantity values (magnitudes with associated units).

Figure 9 displays the elements of calibration for a linear relationship based on an idealized chromatographic analysis for 24R,25-dihydroxyvitamin D₃ calibrated with SRM 2971 24R,25-Dihydroxyvitamin D₃ Calibration Solution.⁹⁸ This SRM delivers the analyte at a certified mass fraction of $(1.054 \pm 0.019) \mu\text{g/g}$, about a factor of 200 times greater than the expected range in normal human sera. The working calibration solutions are prepared by gravimetric dilution into the solvent used for routine samples. In addition to the uncertainty in the certified value, these preparatory steps contribute to the uncertainty in the mass fraction of analyte in the working standards.

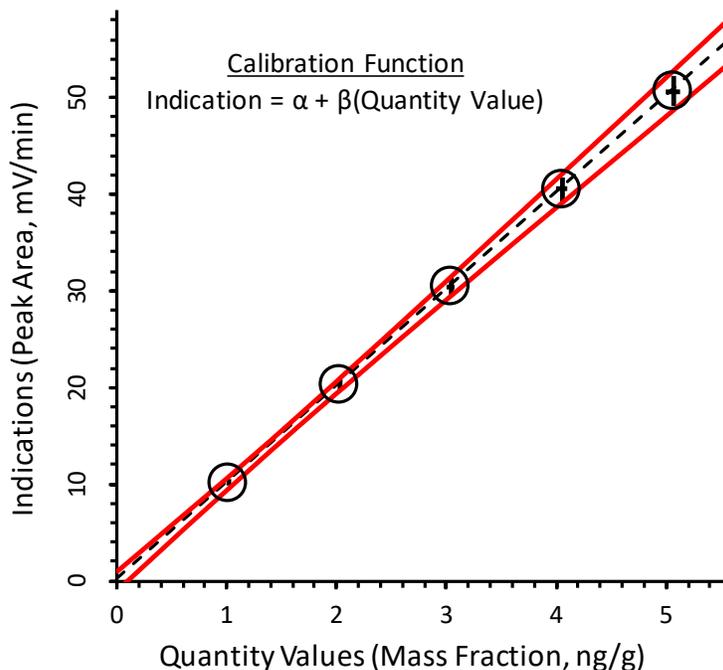


Figure 9. Quantity Values, Indications, and Calibration Function

The crosses with the open circles represent 95 % expanded uncertainties on the measured indications (here, chromatographic peak areas measured in mV/min) and calibration points (here, solutions prepared by gravimetric dilution of an SRM with analyte mass fractions expressed in $\mu\text{g/g}$). Calibrant quantities are plotted along the horizontal (X) axis; indications are plotted along the vertical (Y) axis. The dashed black line represents the linear calibration function: $Y = \alpha + \beta X$. The solid red curves represent the 95 % uncertainty interval on the function. In this example, the values of the α and β parameters are $(0.04 \pm 0.50) \text{ mV/min}$ and $(10.00 \pm 0.30) (\text{mV/min})/(\text{ng/g})$, respectively; the correlation between the α and β parameters, $r(\alpha, \beta)$, is -0.85.

Note: Classical regression (the technique widely available in spreadsheets) assumes the values of the independent variable(s), x , are known exactly and those of the dependent variable, $y \pm u(y)$, are probability distributions. Therefore, classical regression represents indications as a function of known quantities: $Y = \alpha + \beta X$. The inverse of the calibration function, here $X = (Y - \alpha)/\beta$, is then used to predict the quantity of an unknown from its measured indication. Various implementations of generalized distance regression (GDR) (also called generalized least squares (GLS), total least squares (TLS), errors-in-variables (EiV), etc.), where both the dependent and independent variable are defined as probability distributions rather than fixed values, are available but require specialized software.^{44,45,46,47} GDR treats instrumental indications and the quantity values of the measurand in the calibrants symmetrically, hence affords the opportunity to build the analysis function directly, instead of as the mathematical inverse of the calibration function. NIST employs this approach routinely for value assignment and uncertainty quantification for gas mixture CRMs.⁴⁴

2.9.2. Method/Procedure/Process Validation (and Verification)

The VIM defines validation as “verification, where the specified requirements are adequate for an intended use” [VIM3:2.45] where verification is defined as “provision of objective evidence that a given item fulfills specified requirements” [VIM3:2.44]. ASTM E2857 Standard Guide for Validating Analytical Methods provides a more pertinent definition: “confirmation, by the provision of objective evidence and examination, that a method meets performance requirements and is suitable for its intended use.”⁴⁸ As used in this document, validation and verification are regarded as synonyms. Both terms refer to the collection, documentation, and presentation of evidence that the performance of a method/procedure/process is fit for purpose.

Figure 10 displays one approach to validation, treating a validation CRM as an unknown and comparing the measurement result with the certified value. A sample of SRM 2973 Vitamin D Metabolites in Frozen Human Serum (High Level)⁸¹ is analyzed as an unknown. The certified 24R,25-dihydroxyvitamin D₃ mass fraction delivered by this material is (3.06 ± 0.11) ng/g. The peak area is evaluated as (30.6 ± 1.1) mV/min. Using the calibration function summarized in Figure 9, the mass fraction is estimated to be 3.06 ng/g. Since the calibration function’s uncertainty contributes to the predicted value, the 95 % expanded uncertainty on this result is 0.24 ng/g. The excellent agreement between the measured and certified values provides evidence the procedure is valid.

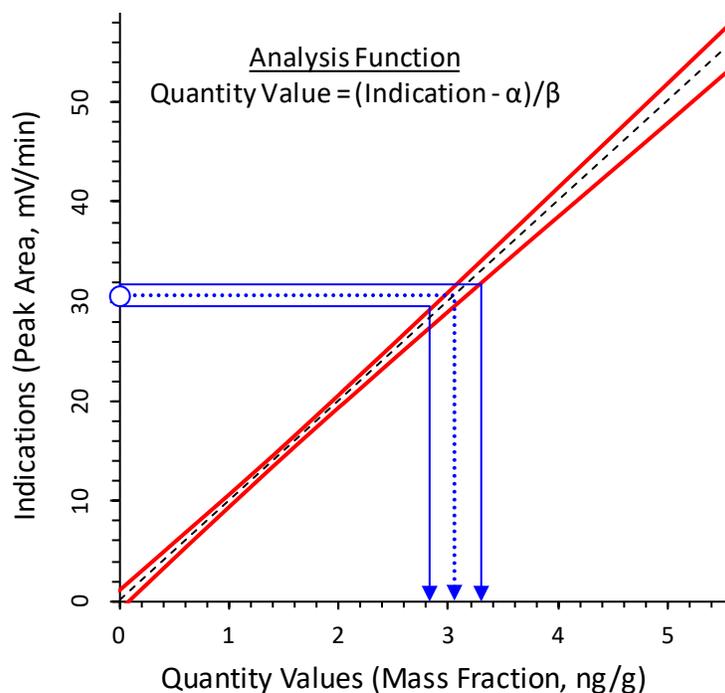


Figure 10. Quantity Values, Indications, and Analysis Function

The open circle represents a measured indication (here, a chromatographic peak area measured in mV/min) and its 95 % expanded uncertainty. The dashed black line represents the linear calibration function: $Y = \alpha + \beta X$. The solid red curves represent the 95 % uncertainty interval on the function. The dotted blue line represents the linear prediction function: $X = (Y - \alpha) / \beta$. The solid blue lines represent the propagation of the indication and calibration function uncertainties.

Note: the uncertainty contributed by the calibration function established in Figure 9 could be reduced by using more (or more strategically located) working calibration solutions.

2.9.3. Method/Procedure/Process Independence

The certification modes described in Section 3 require there to be fit-for-purpose agreement between two or more independent sources of information. Like fitness for purpose, “independence” is a relative concept for which there is no simple definition.

Complete analytical orthogonality (fundamentally different measurement principles) is seldom necessary even when possible. It often suffices that the most problematic steps in a process be thoroughly investigated using methods that are as different as resources permit. For instance, using different chromatographic columns, mobile phases, and detection modes may provide adequately independent evidence for the absence of co-eluting organic components in a simple calibration mixture. However, demonstrating that results are independent of the “pre-analytical” sampling, extraction, and transformation steps in a process may be the critical consideration for analytes in complex matrix materials.

Appropriate training, experience, and good judgement are keys to achieving – and recognizing – adequate independence.

2.9.4. Reference Measurement Procedure (RMP)

A reference measurement procedure (RMP) is formally defined as a “measurement procedure accepted as providing measurement results fit for their intended use in assessing measurement trueness of measured quantity values obtained from other measurement procedures for quantities of the same kind, in calibration, or in characterizing reference materials” [VIM3:2.7]. In this document, an RMP is a measurement procedure that has been extensively characterized and found capable of providing accurate, metrologically traceable results for a measurand of interest. RMPs are insensitive, at least within established limits, to the sample matrix. This is particularly true of RMPs for many inorganic analytes, where one of the first steps in the analysis is to change the form of the sample to eliminate or greatly reduce the influence of the original matrix; e.g., acid digestion, thermal decomposition, or borate fusion.

Note: The development of a fit-for-purpose RMP (and the demonstration that it is indeed fit for the intended purpose) basically involves assessing precision and bias over the analytical range of interest. How to accomplish this is well beyond the scope of this document. However, a wealth of opinion and guidance is available: see references 48, 49, 50, 51, 52 and their references.

2.9.5. Primary Reference Measurement Procedure (“Primary Method”)

A primary RMP is a “reference measurement procedure used to obtain a measurement result without relation to a measurement standard for a quantity of the same kind” [VIM:2.8]. The key phrase here is “a quantity of the same kind,” meaning that the RMP *does not require calibration with a reference material for the same analyte*. However, reference may be made to measurement standards for other quantities that influence the RMP, e.g., mass, temperature, time, etc.

For example, coulometry is a potentially primary method for determining amount of substance. It involves counting the number of electrons consumed in a reaction. To determine the amount of cyclohexane added to a solution of potassium bromide, two measurements are required: the applied electric current (coulombs per second) and the time (seconds) required for every molecule of cyclohexane to capture two bromine ions. Combining these measured values with the reciprocal of the Faraday constant (moles of electrons per coulomb) provides the cyclohexane amount in moles. This measurement method involves reference to standards of time and electrical current, but not to standards for the concentration of cyclohexane.

2.9.5.1. Primary Direct Reference Measurement Procedures (“Primary Direct Method”)

Primary direct RMPs provide values that are directly traceable to SI units or the natural unit “count one.” Examples of primary direct RMPs are: gravimetry (mass), coulometric titrimetry (mol/kg), and digital polymerase chain reaction (count of targeted entities per partition volume).

2.9.5.2. Primary Ratio Reference Measurement Procedures (“Primary Ratio Method”)

Primary ratio RMPs provide values that are the ratio of two values of the same quantity. Examples of primary ratio RMPs are: spectrophotometry (luminous intensity between when the sample is in and out of the light path), internal standard ¹H-qNMR (¹H-content of test sample and an internal standard of known composition), and ID-MS (signal intensity between test and isotopically labeled analyte).

2.9.5.3. “Primary” Versus “Definitive” Versus “Always Accurate”

It is sometimes asserted that certain “primary” or “definitive” analytical methods “irrefutably” provide accurate (i.e., true) results.⁵³ This is an unrealistically trusting viewpoint. There may be differences between what an RMP is capable of and how it is used in a given application.⁶³ “Potentially definitive” is a more appropriate non-technical term for RMPs that are expected to provide unbiased results.

The term “primary method” should only be used for methods that do not require a calibrant of the same kind as the sample.

2.9.6. Higher-Order Reference Measurement Procedure

To be considered a NIST higher-order RMP, a [primary direct](#) or [primary ratio](#) RMP must be documented in detail and published in a peer-reviewed form accessible to the public.

2.9.7. Field Measurement Procedure

In this document, “field” measurement procedures either have not been adequately characterized for use in value assigning NIST materials or are unacceptably sensitive to the sample matrix. Field procedures may provide significantly inaccurate results depending on the presence (or absence) of non-analyte chemical components or physical characteristics of the sample.

2.10. Measurement Uncertainty

The NIST Quality Manual for Measurement Services⁶ Section 3 defines measurement uncertainty as the doubt about the true value of the measurand that remains after making a measurement. It explains that measurement uncertainty is described fully and quantitatively by a probability distribution on the set of values of the measurand: at a minimum, it may be described summarily and approximately by a quantitative indication of the dispersion (scatter) of such distribution. See Reference 8 for further information.

2.10.1. Level of Confidence

The JCGM 100:2008 Guide to the Expression of Uncertainty in Measurement (GUM)⁹ Section 6.2.2 recommends “coverage probability” or “level of confidence” to describe the proportion of values of the measurand that are believed to lie within the “range of values within which the ‘true value’ is asserted to lie with a stated level of confidence.” [ISO Guide 30:3.4] In keeping with [ISO 17034:2016:3.2] usage, this document uses “level of confidence.”

For scalar measurands, the GUM and NIST’s Simple Guide for Evaluating and Expressing the Uncertainty of NIST Measurement Results (NIST’s Simple Guide)⁸ refer to the “range of values” as the “coverage interval.” The Simple Guide generalizes the concept to “coverage region” for more complex measurands.

2.10.2. Stated Levels

While specific levels of confidence are not mandated, JCGM 100:2008 GUM⁹ Section 4.3.4 recognizes “90, 95, or 99 percent” as levels that “one may find.” The 95 % level is by far the most often encountered. As NIST’s Simple Guide states “In most cases, specifying a set of values of the measurand believed to include its true value with 95 % probability (95 % coverage region) suffices as expression of measurement uncertainty.”⁸ Why 95 %?

- **Recognition:** The interval $x \pm 2u$ is widely recognized as an approximate 95 % level of confidence interval for Gaussian (normal) probability distributions of mean x and standard uncertainty u . While the “exact” 95 % interval is $x \pm 1.96u$, the slight overestimate from rounding 1.96 up to 2 does no harm and greatly simplifies customer communications.
- **Practicality:** The greater the asserted level of confidence, the more evidence needed to describe the tails of the probability distribution that generated the set of measurand values. Describing the central 95 % of the set provides “in most cases” a practical compromise between benefit and cost.
- **Limitation of the normal model:** The 5 % of measurand values outside the 95 % interval often includes values that are much further outside than expected for a truly Gaussian distribution.

2.10.3. Uncertainty for Non-Certified Values

As discussed in Section 1.2.1, NIST provides non-certified values only when the measurand identity, homogeneity, and stability have been established as fit-for-purpose, but the values' accuracy (trueness and precision) have not been confidently established.

The uncertainty associated with a quantitative non-certified value should characterize the known variability components (typically repeatability or reproducibility precision, homogeneity, and stability). The documentation associated with the value should describe these components in enough detail for a user to have confidence in the suitability of the material for use in harmonization, method development, or quality control. However, if the true value of the measurand is not sufficiently well established to certify the value, the documentation must not imply that the true value is contained within an interval at any level of confidence.

All quantitative values delivered by an RM must be documented as non-certified regardless of how confidently the accuracy has been established. If one or more values of major interest in a material can be sufficiently well established, the RM should be upgraded to an SRM and the values certified.

2.11. Identification Confidence

A conventional probabilistic evaluation and expression of measurement uncertainty is not appropriate for expressing the confidence in a statement of the chemical or biological identity of the measurand in an SRM. For identity, NIST now uses a three-level ordinal scale of confidence:

- Highest Confidence: There is enough evidence to make the identification with no unresolved ambiguities or contradictions.
- Confident: There is enough evidence to make the identification, albeit with technical ambiguities that are explicable but not fully resolvable.
- No confidence: There is not enough evidence to establish the trustworthiness of the identity.

Figure 11 displays a flow diagram of the confidence assessment process. What constitutes “enough evidence” and “fully resolved” are issues to be determined by the measurement communities concerned.⁴²

Identities can be certified only when the assessed confidence is “Highest.” The “Highest confidence” assessment is reserved for certified identities.

2.11.1. Confidence for Non-Certified Identities

Non-certified identities are provided only when assessed as (at least) “Confident” according to explicitly stated criteria. When there are multiple measurands (e.g., for metabolomic-related RMs), identifications based on different criteria are listed in separate Tables.

All identities delivered by an RM must be documented as “Confident” regardless of how confidently the identity has been established. If one or more identities are of major interest in a material and can be established with “Highest Confidence,” the RM should be upgraded to an SRM and the identities certified.

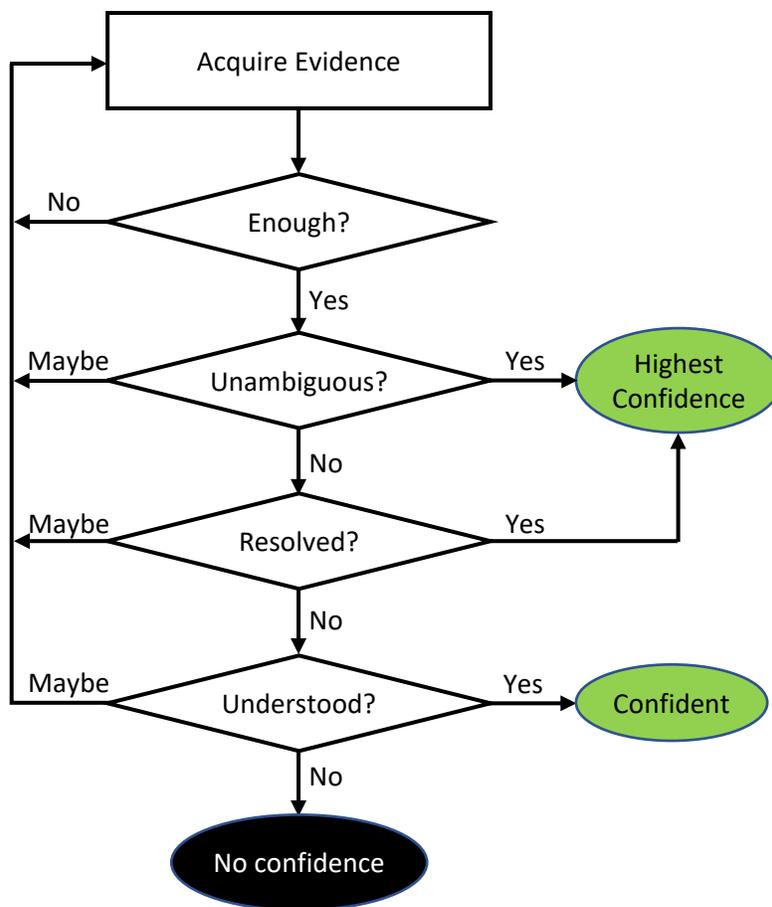


Figure 11. Process for Establishing the Confidence in an Assigned Identity

It is often difficult to establish what is “enough” evidence before quite a lot of evidence has been acquired. If some of these initial data are contradictory, further action is required – typically acquiring additional evidence – to resolve the ambiguities. Highest Confidence can only be achieved if all ambiguities in the initial (and any subsequent) data are fully and confidently resolved (e.g., as misinterpretations, artifacts, or under-appreciated limitations of a measurement process). If defensible root-causes for the ambiguities can be established but definitive evidence cannot be acquired, “Confident” but not “Highest Confidence” identification can be established. If the root-causes of the ambiguities cannot be identified, identification cannot be established with any confidence.

Establishing chemical/biological identity requires a fit-for-purpose determination of chemical structure/biological taxonomy. These determinations are not amenable to the usual “95% level of confidence” assessment; rather confidence in the identification is based on community standards about what constitutes fit-for-purpose evidence. The assessment is intrinsically binary: there either is or is not enough pertinent and consistent evidence to certify with “Highest Confidence” that the community standards have been met. This is not a probabilistic determination, rather a judgement based on expert interpretation of information from multiple sources.

2.12. Metrological Traceability

Metrological traceability is now formally defined as 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” [VIM3:2.41]. The more general (and more directly appropriate for many chemical and biological measurands) term “chain of comparisons” was used in VIM2.³³ However, “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 [VIM3:2.42 Note 3]. The metrological traceability of the results from many types of chemical measurement is detailed in reference 54.

2.12.1. “Traceable to NIST”

“Traceable to NIST” is shorthand for and should be gently corrected to “Traceable to the SI through measurement results certified by NIST.”

The NIST policy on traceability includes the following:⁵⁵

- The provider of the result of a measurement is responsible for supporting its claim of the traceability of that result or value. This is the case whether that provider is NIST or another organization.
- The provider of a measurement result must document the measurement process and uncertainty estimates used to establish the claim and provide a description of the chain of calibrations that were used to establish a connection to a specified reference.
- The user of the result of a measurement is responsible for assessing the validity of a claim of traceability.

2.12.2. Traceability Chain

A metrological traceability chain is the “sequence of measurement standards and calibrations that is used to relate a measurement result to a reference” [VIM3:2.42]. Descriptions of a traceability chain must include the calculations and uncertainty estimates used to establish the relationship.

The following entries present generic graphical representations of the traceability chains for results traceable to reference systems through NIST SRIs, PSs, and SRMs. Figure 12 presents the simple chain appropriate to SRI results and Figure 13 presents the chain for results that trace through SRM calibrants.

In the absence of a suitable calibration CRM, metrological traceability can be established by calibrating with a matrix material that delivers a certified value for the measurand of interest. However, the traceability chain for a matrix material has at least one more link than that of a calibration material and so will not provide the smallest possible measurement uncertainty. Calibrating with a matrix material may also lead to biased results unless the measurement procedures used are known to be relatively insensitive to the composition of the matrix. Figure 14 presents the partial chain when field procedure results trace through a matrix SRM.

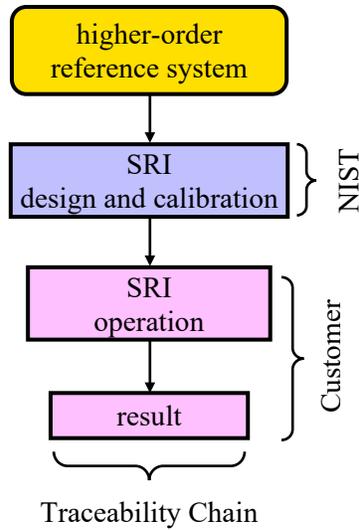


Figure 12. Metrological Traceability of Results from a NIST Standard Reference Instrument (SRI). Arrows represent links in the calibration chain; the direction of the arrows indicates the inheritance path. NIST establishes that measurement results provided by the SRI are traceable to the higher-order reference system (typically the SI) when the reference instrument is maintained and used as directed by NIST. It is the customer's responsibility to establish traceability by documenting that the SRI is properly operated and maintained.

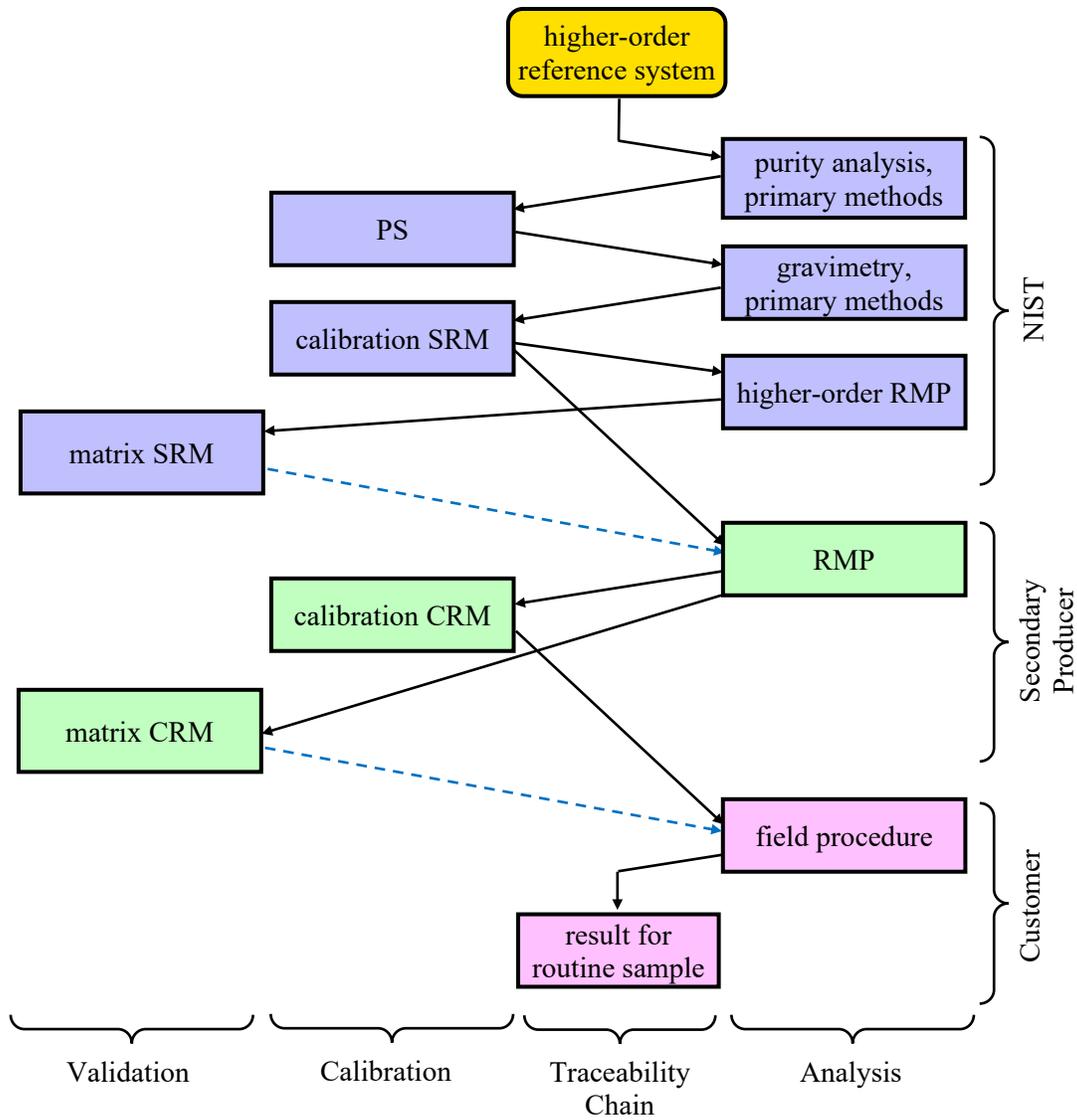


Figure 13. Metrological Traceability of Results Using NIST’s Reference Materials

Solid arrows represent links in the calibration chain; dashed arrows represent validations. The direction of the arrows indicates the inheritance path. NIST establishes that the certified values delivered by its Standard Reference Materials (SRMs) are traceable to the higher-order reference system (typically the SI) when properly stored and used. However, SRMs are intended to be used by secondary standards producers and other expert customers to calibrate and validate RMPs that they use to value-assign customer-oriented calibrant and validation materials. It is the secondary producer’s responsibility to establish the traceability of the assigned values. It is the customer’s responsibility to establish the traceability of their measurement results by documenting that their measurement procedure is appropriately calibrated and validated.

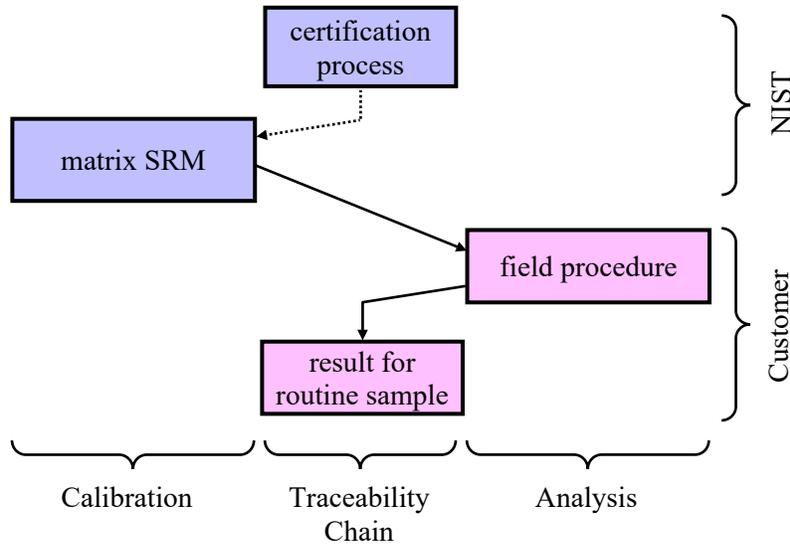


Figure 14. Metrological Traceability of Results When a Matrix Material is Used as a Calibrant

Solid arrows represent links in the calibration chain; the dotted arrow represents a contingent linkage. The direction of the arrows indicates the inheritance path. When a measurement procedure is calibrated using a matrix SRM, the results produced for a routine sample are metrologically traceable to the SRM. It is the customer’s responsibility to determine if the measurand realized by the field procedure is the same as that realized by the certification process. If identical, the traceability of the result can be extended to the SRM’s reference system. If not identical, the result of the field procedure may be subject to bias due to the measurand mismatch.

2.12.3. Commutability

CRM commutability is formally defined as the “property of a reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two given measurement procedures, and the relation obtained among the measurement results for other specified materials” [VIM3:5.15]. More generally, it is the “property of a reference material, demonstrated by the equivalence of the mathematical relationships among the results of different measurement procedures for a [reference material] and for representative samples of the type intended to be measured” [ISO Guide 30:2015:2.20]. However, the spirit of the concept is more directly captured by a definition from clinical literature: “... a property of a reference material such that values measured for that reference material and for representative clinical samples have the same relationship between two, or more, measurement procedures for the same measurand.”⁵⁶ That is, for clinical CRMs commutability refers to how well the CRM mimics the properties of clinical samples.⁵⁷

Unfortunately, these definitions fail to recognize that commutability is a property of *interactions* between reference materials and specific measurement procedures, not the materials in isolation. Different procedures may be influenced by different interferences. Materials that are realistically representative of typical sample materials for some procedures may not be for others. Establishing the commutability of a CRM among any fixed set of procedures does not ensure that it will be suitable for the next procedure. It is impossible to design a CRM that is inherently commutable; however, understanding the operational principles and potential interferences of the measurement procedures for which the CRM will be used increases the likelihood that the CRM will be fit for purpose.

Most NIST matrix SRMs are intended to help validate the RMPs of secondary standards producers and other users who prepare metrologically traceable reference materials suitable for use with their own procedure(s). Therefore, the certification modes described in Section 3 are intended to ensure that NIST's materials are commutable among RMPs that are relatively insensitive to differences in sample matrix. Figure 15 displays the two commutability domains in the traceability chain.

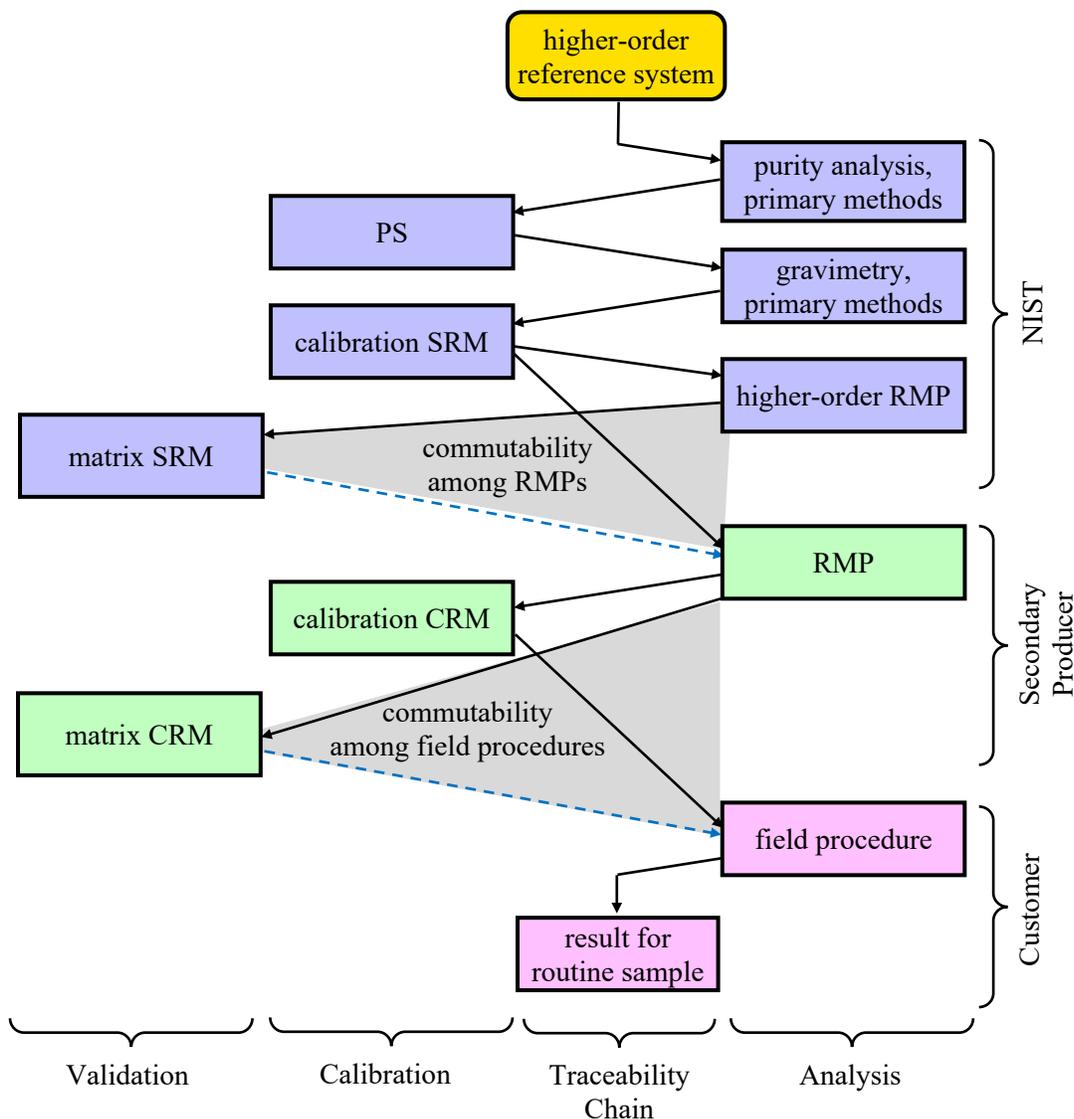


Figure 15. Commutability Responsibilities for Producers and Users of Matrix CRMs

Solid arrows represent links in the calibration chain; dashed arrows represent validations. The direction of the arrows indicates the inheritance path. SRMs are designed to be commutable among reference measurement procedures (RMPs), that is procedures that are relatively insensitive to non-target components of the matrix. They are not designed to be commutable among field measurement procedures. Evaluating the commutability of CRMs designed for use with field procedures is the responsibility of the procedures' developers and users.

Some matrix CRMs are used by manufacturers to verify calibration of their routine measurement procedure. In this case, it is the manufacturer's responsibility to ensure that the CRM is suitable for use as a trueness control.

2.12.4. Standardization and Harmonization

In a metrological context, standardization is used for the process of modifying measurement procedures to provide true values. Harmonization is used when the goal is to bring procedures into agreement even when truth is unknown. Metrological traceability to an international harmonization protocol provides a “highest-practical-order reference system” when no other approach is practical. SRMs are intended to support standardization efforts. RMs are intended to support harmonization efforts.

2.12.5. Trackability

While “trackability” is sometimes misused as a synonym for metrological traceability, the colloquial sense of “ability to be tracked” does have metrological utility as the chronological history of materials and their associated documentation: who has it, where is it, and under what conditions is it stored. The current phase “farm-to-fork traceability” is an example of the colloquial usage.⁵⁸

2.13. Reference Material

The VIM3 and ISO Guide 30:2015 definitions for the general class of reference materials are congruent:

- material, sufficiently homogeneous and stable with reference to specified properties, which has been established to be fit for its intended use in measurement or in examination of nominal properties [VIM3:5.13].
- 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 [ISO Guide 30:2015:2.1].

Note: This document uses the term “measurement” for the determination of all properties, whether quantitative, qualitative (nominal), or somewhere in between (ordinal).

2.13.1. Candidate Reference Material

A candidate reference material is a “material, intended to be produced as a reference material [ISO Guide 30:2015:2.3]. However, not all that is intended necessarily comes to pass. The terms “Candidate SRM” or “Candidate RM” can be used within NIST when referring to such materials in internal documents. No material is to be referred to as a “candidate” material in an external publication by a NIST author.

2.13.2. Certified Reference Material (CRM)

The VIM and ISO Guide 30:2015 definitions are congruent, but differ in their emphasis:

- reference material, accompanied by documentation issued by an authoritative body and providing one or more specified property values with associated uncertainties and traceabilities, using valid procedures [VIM3:5.14]
- reference material characterized by a metrologically valid procedure for one or more specified properties, accompanied by an [reference material] certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability [ISO Guide 30:2015:2.2]

This document follows the Guide 30:2015 definition with its emphasis on documentation.

2.13.3. Matrix Reference Material

ISO Guide 30:2015:2.4 states that a matrix reference material is “characteristic of a real sample” with Notes that they:

- are intended to be used in conjunction with the analysis of real samples of the same or a similar matrix,
- may be obtained directly from biological, environmental, or industrial sources,
- may be prepared by spiking the component(s) of interest into an existing material,
- are not chemical substances dissolved in pure solvent.

Since what constitutes a “real sample” is contingent on the material’s intended purpose, this definition is overly restrictive. The concept of real samples applies equally to “natural” samples and to created materials like alloys if the measurand they deliver is fit for the intended purpose(s). Relative to the purpose(s), NIST matrix materials are as like “real samples” as is practical given the need for homogeneity, stability, and production of suitable numbers of units.

Note: The term “natural-matrix material” is sometimes used to distinguish between materials with “complex” (e.g., tissues, soils, alloys) and “simple” (e.g., hexane, acidified water, pure metals) matrices. Given that the distinction between simple and complex depends on the intended purpose, this document does not distinguish between natural (native) and unnatural (purpose-created) matrices.

2.13.4. Primary Standard

In this document, PSs are nominally single-component solids or liquids or simple mixtures of gases that have been value-assigned with a fit-for-purpose purity and fit-for-purpose measurement uncertainty. The purity assessment process used to assign the value and its uncertainty provides linkage to a higher-order reference system.

PSs need not be of the highest feasible purity nor exhaustively characterized, just of high enough purity and characterized well enough to be fit for their intended purpose.^{59,60} The PS1 qNMR standard was designed to be the ultimate link between the SI and qNMR purity results for virtually all hydrogen-containing small organic compounds.⁸⁷ To be fit for this purpose, the material was exhaustively (and expensively) characterized with all relevant analytical methods and a novel mathematical approach developed to combine the resulting information. The PS1 benzoic acid mass fraction is certified to be 999.92 mg/g with a 95 % level-of-confidence expanded uncertainty of 0.05 mg/g (0.005 % relative). Producing a single-element PS that can be used to produce a calibration solution having a fit-for-purpose 95 % expanded relative uncertainty of 0.2 % would require less effort.

2.13.5. Validators and Calibrants

For each measurement procedure, a CRM can only be used either as a calibration standard or in a validation role. Re-analyzing a CRM that was used to calibrate a procedure can only “validate” whether the procedure is stable and whether the data analysis is working.

A calibration CRM (calibrant) is a “reference material used for calibration of equipment or a measurement procedure” [ISO Guide 30:2015:2.21]. Most NIST SRMs intended for use in calibration, especially when using NIST measurement procedures, are nominally “pure” compounds or simple mixtures of one to a few compounds. The intended purpose of calibrant SRMs is to provide higher-order reference system metrological traceability to the results of methods that have been calibrated with them. That means the uncertainty of the assigned value must be propagated, and the measurand certified must match the measurand of the measurement procedure being calibrated.

Matrix CRMs may be a defensible choice for calibration of a measurement procedure. This approach is frequently used for field measurements, especially with measurement procedures that require calibrants to be as similar to samples as possible. The approach is used at NIST on occasions when an independent or confirming analysis is needed when no NIST RMP has been developed and resources are limited. As an example, XRF can be calibrated for mass fractions of elements in food and dietary supplement materials. Because NIST has not developed a sample preparation approach to overcome matrix composition biases for these complex materials, it is expedient to calibrate the spectrometer using a set of carefully selected matrix SRMs of other types, with both calibrants and samples made into pressed briquettes. Establishing uncertainty estimates and traceability statements for these results may be less rigorous than for higher-order RMPs, but they are fit for their intended purpose.

A validation CRM (validator) is simply one intended for use in validating measurement procedures. Most validators have relatively complex matrices because laboratories need to convince clients and third-party auditors that validation has been accomplished with a CRM very close in composition to the organization's products. Sometimes NIST has a similar need when an RMP must be shown to be free of bias.

The concepts of calibration and validation are blended in VIM3:2.42, Note 3: "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." Here, one reference material is the calibrant and one is a validator. The verb "to check" means to validate, and "to correct" is to alter the calibration. Even when a bias is detected, it is preferable to improve the method and to identify and eliminate the bias rather than to apply corrections for selected materials.⁶¹ Corrections come with additional uncertainty because of assumptions that must be made and complicate both the measurand definition and traceability link(s).

Because there may be only one CRM that provides a composition within the scope of measurement, an analyst may be faced with the need to decide whether to calibrate with the CRM or to validate with it. If the measurement procedure requires use of a matrix CRM as a calibrant to avoid sample matrix bias, there will be no direct way to validate the method. In this situation, the analyst may wish to consider alternative calibration models that enable calibration using a PS, such as standard additions.⁶² Standard addition methods exploit changes in instrumental response with added analyte to estimate the quantity of the analyte originally in the sample. When the added analyte does not significantly alter the sample matrix and the relationship between the quantity and the instrument response is well-defined, this can provide bias-free use of a calibrant CRM thus freeing the matrix-matched CRM for use in validation. ISO/IEC 17025:2017 *General requirements for the competence of testing and calibration laboratories*² Section 7.2.2.1 suggests several alternative approaches for validating a calibrated method.

2.14. Secondary Standard Producer

For the purposes of this document, a secondary standard producer is defined as any (suitably accredited) CRM-producing organization that uses NIST (or another NMI) CRMs or higher-order RMPs to establish the metrological validity and traceability of their products. Secondary standard producers thus leverage the commercial and scientific impacts of the NMI products.

3. Certification Modes

The following sections describe the approaches or “modes” NIST currently uses or anticipates using for certifying values for its PS, SRM, RGM, and NTRM tools. The descriptions present minimal requirements along with illustrative examples. These descriptions replace those described in previous documentation.¹

Determining which approach is “best” for a given certification depends upon the resources (including people, time, appropriate equipment, and money) required to certify the value as well as the tool’s purpose. Having a clearly stated need is the first and most important step in deciding how to efficiently provide a fit solution. This decision is critical when beginning projects but does not preclude revising the scope when circumstances change.

Since there is considerable overlap among some of the characterization modes, differing more by how analytical results are used to assign values rather than how they are obtained, the measurement procedures used to certify a given value are sometimes a hybrid of two (or more) of these modes. NIST CRMs that deliver multiple certified values need not (and often do not) use the same procedures for all measurands.

3.1. One Higher-Order Reference Measurement Procedure at NIST

Certification at NIST using a single higher-order [reference measurement procedure](#) ([higher-order RMP](#)) for the measurand of interest requires that:

- the RMP be formally documented in a publicly accessible form,
- all potentially significant sources of uncertainty have been evaluated for the measurand of interest, and
- the results of the RMP are independently confirmed.

Confirmation can be achieved by:

- comparison of results from suitably independent measurements performed by NIST, by one or more expert collaborating laboratories, in an ILS, or by demonstrating the performance of the RMP through analysis of an existing CRM for the same measurand and similar composition.

The required level of agreement between the higher-order RMP and validation information must be predetermined.^{63,64}

This mode is appropriate for materials that deliver a measurand that can be accurately determined by the higher-order RMP, at a level known to be within the analytical range of the procedure, and with an uncertainty that is [fit-for-purpose](#). Results from that determination are frequently confirmed using one or more relatively independent (if of less high-order) measurement procedures. Examples include:

- **SRM 660c Line Position and Line Shape Standard for Powder Diffraction (Lanthanum Hexaboride Powder)**^{65,66}
This SRM is certified with respect to lattice parameter and, as such, it is used to calibrate equipment with regard to profile position. It has been prepared to display a minimal level of microstructure-induced profile broadening; its primary function is to determine the peak shapes associated with the diffraction equipment itself. The use of SI-traceable emission spectra provides the certified lattice constants with a linkage to the fundamental unit of length, the meter.⁶⁷ The angular scale of the measured peaks is provided via a high-precision optical angular encoder. These measured angles are also affected by an instrumental aberration function, which is determined from the known instrument geometry and the use of the Fundamental Parameters Approach.^{68,69} Thus, all components of the measurement are directly traceable to first principles.
- **SRM 931h Liquid Absorbance Standard for Ultraviolet and Visible Spectrophotometry**^{70,71}
This SRM is intended for critical evaluation of daily working standards used in spectrophotometry and for use as an accuracy check of the photometric scale of

spectrophotometers that provide a narrow effective spectral bandpass. Each SRM 931h unit consists of three cobalt-nickel liquid filter solutions at different concentrations and a blank solution. The certified net absorbances, corrected for the absorbance due to the blank solution, are determined using primary ratio measurements made at NIST. Results are verified through evaluation of selected sets of glass absorbance filter SRMs.

- **SRM 1720 Northern Continental Air**^{72,73,74,75}
Single-analyte primary standard (PS) gas mixture suites that span concentrations of analytical interest are produced from well-characterized starting materials using the primary direct method of gravimetric preparation. SRMs, such as the natural-background air SRM 1720, are value-assigned relative to the NIST gas PSs (a primary ratio method). The assigned values were verified by comparison to results provided by the Earth System Research Laboratories of the National Oceanic and Atmospheric Administration (NOAA), Boulder, Colorado, a designated institute of the World Meteorological Organization. SRM 1720 is intended for calibrating instruments used for ambient carbon dioxide and other trace gases.
- **SRM 1934 Fluorescent Dyes for Quantitative Flow Cytometry (Visible Spectral Range)**^{76,77}
This SRM is intended for use by stakeholders in the quantitative flow cytometry community to assign fluorescence intensity values to calibration microspheres for fluorescence channels of flow cytometers in the visible spectral range. It is also used internally by NIST to make similar assignments for members of the Flow Cytometry Quantitation Consortium. The SRM consists of fluorescent solutions certified for fluorophore concentration and purity. Primary ratio qNMR spectrometry was used as a primary method to determine the mass purity of each fluorophore. The purity was independently verified by analysis of impurities using a variety of other analytical techniques.
- **SRM 2374 DNA Sequence Library for External RNA Controls**⁷⁸
This External RNA Controls Consortium (ERCC)-sponsored SRM delivers 96 unique double-stranded DNA nucleotide sequences. Use of these materials as external controls supports confidence in gene expression assays by providing quantitative assessment of the technical performance of gene expression measurements. For each control, complete Sanger sequencing of both strands was performed on replicate samples. The resulting data were independently hand-curated and evaluated for both sequence and confidence estimation by two analysts. Discrepant results were resolved using two independent, ultra-high throughput, short-read sequencing experiments performed on two different platforms.
- **SRM 2924 C-Reactive Protein Solution**^{79,80}
This SRM is intended for use in calibrating procedures and devices for the determination of C-reactive protein (CRP), an inflammation marker in human serum. The molar concentration of CRP was determined by primary ratio amino acid analysis using isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) and verified using a contemporaneously developed CRM produced by the National Metrology Institute of Japan.
- **SRM 2973 Vitamin D Metabolites in Frozen Human Serum (High Level)**^{81,82,83}
SRM 2973 is intended to be used as an accuracy control in the critical evaluation of methods for determining the concentration of vitamin D metabolites in human serum. The concentration of 25-hydroxyvitamin D₃ (25(OH)D₃) in serum is an indicator of vitamin D status; that of 24R,25-dihydroxyvitamin D₃ (24R,25(OH)₂D₃) is a catabolism marker and an indicator of kidney disease.⁸⁴ Certified values for 25(OH)D₃ and 24R,25(OH)₂D₃ are based on results from ID-LC-MS/MS procedures recognized as higher-order reference measurement procedures by the Joint Committee for Traceability in Laboratory Medicine (JCTLM). SRM 2973 was distributed as a blinded study material in a 2014 ILS; results confirmed the accuracy of the NIST results and the suitability of the material as an analytical accuracy control.

- **SRM 3037 Arsenous Acid (AsIII) Standard Solution**⁸⁵

SRM 3037 is a primary calibration standard for the quantitative determination of arsenous acid, a water-soluble arsenic species. An acidified aqueous solution was gravimetrically prepared from arsenic trioxide to contain a known mass fraction of arsenous acid. The mass fraction of arsenic III in the solution was determined using gravimetric titrimetry. The titrant was determined using a primary ratio method, relative to SRM 83d Arsenic Trioxide (Reductometric). SRM 83d was certified using a primary direct coulometric titrimetry RMP. Impurity arsenic species were measured by ion chromatography-inductively coupled plasma mass spectrometry (IC/ICP-MS) and liquid chromatography-inductively coupled plasma mass spectrometry (LC/ICP-MS).

3.2. Two or More Independent Reference Measurement Procedures at NIST

Value-assignment can be based on NIST results from two or more relatively independent, NIST-characterized reference measurement procedures (RMPs, but not necessarily higher-order RMPs).⁸⁶ While RMPs rarely have completely different sources of uncertainty, the procedures are chosen to minimize similarities between methods of sample preparation and analysis and to provide analytical responses using [fit-for-purpose](#) different physical, spectroscopic, or chemical phenomena. The measurement uncertainty associated with the combined result includes a component estimating bias as a persistent between-method difference.

This mode is appropriate whenever NIST has implemented and critically evaluated two or more suitable RMPs for the measurand. Examples include:

- **NIST PS1 Primary Standard for Quantitative NMR (Benzoic Acid)**⁸⁷

High-purity benzoic acid was value-assigned using primary direct coulometric acidimetry and primary ratio qNMR spectrometry. Confirmatory evidence was provided by the close agreement with a mass-balance estimate based on the amount of water as determined by Karl Fischer titration and non-volatiles by ash analysis, and the absence of organic solvents and structurally related impurities from diverse analytical techniques. This material is intended to provide the ultimate metrological traceability link between the SI and chemicals inherently determinable by qNMR.

- **Sodium in SRM 956d Electrolytes in Frozen Human Serum**^{88,89}

This SRM is intended for use in validating clinical analysis procedures for the determination of electrolytes in human serum or plasma. The certified concentrations for sodium are based on measurements made at NIST using inductively coupled plasma-optical emission spectrometry (ICP-OES) and ion-selective electrode (ISE) potentiometry.

- **SRM 1003c Glass Beads – Particle Size Distribution**⁹⁰

This SRM is intended for use in the evaluation and calibration of equipment used to measure particle size distributions in the 20 μm to 50 μm diameter range. The cumulative mass distribution as a function of particle diameter was certified from 18.8 μm to 43.3 μm as the average of results from laser light scattering (LLS) and electrical sensing zone (ESZ) RMPs. The consensus values were verified using scanning electron microscopy (SEM) analysis of several thousand beads.

- **SRMs 1649b Urban Dust and 1974c Organics in Mussel Tissue (*Mytilus edulis*)**^{91,92,93}

These SRMs are intended for use in evaluating analytical methods for the determination of polycyclic aromatic hydrocarbons (PAHs) and other organic and inorganic measurands in air particulates and biological matrices. Certified values for numerous PAHs were assigned based on NIST measurements using four different analytical techniques based on gas chromatography/mass spectrometry (GC/MS) on different stationary phases and on reversed-phase liquid chromatography (RPLC) with fluorescence detection.

- **SRM 2372a Human DNA Quantitation Standard**⁹⁴
SRM 2372a is intended for use in value-assigning secondary human DNA quantification materials used as daily control materials by human-identification communities. The number concentration of human DNA haploid genomes in aqueous buffer solutions was determined using primary direct chamber and droplet digital polymerase chain reaction (cdPCR and ddPCR) techniques and primary direct measurements of ddPCR droplet volume. The mass concentration of the DNA in these solutions was determined from these measurement results using critically evaluated literature values for nucleotide molar mass and expected number of nucleotides per haploid genome. Variability among multiple independent assays of number concentration is the dominant component of the assigned measurement uncertainty.
- **SRM 2373 Genomic DNA Standards for *HER2* Measurements**^{95,96}
SRM 2373 is a cancer biomarker standard designed to help achieve measurement assurance for precision medicine. *HER2* (official gene name *ERBB2*) is a member of the epidermal growth factor receptor family and is frequently amplified (increased copy numbers) in cancer. Measurement of the amplification of *HER2* gene copy number is important for cancer diagnostics and treatment. Five human breast cancer cell lines with different amounts of amplification were used to prepare high-quality DNA. Determination of the amount of DNA amplification relative to a suite of four reference genes was accomplished using two orthogonal measurement methods, droplet digital PCR (ddPCR) and quantitative PCR (qPCR), using assays targeting different regions of the genes. The qPCR and ddPCR assays were validated using NIST SRM 2372a and a synthetic plasmid containing *HER2* DNA sequences.
- **SRM 2391d PCR-Based DNA Profiling Standard**⁹⁷
This SRM is intended for use in the standardization of forensic and paternity quality assurance procedures for polymerase chain reaction (PCR)-based genetic testing. Human autosomal short tandem repeat (STR) genotypes were certified for 35 autosomal and 7 X-chromosome genetic loci in four unrelated single-source samples and one mixed-source sample and 28 Y-chromosome loci for the three samples that contain male DNA. The genotypes were evaluated at NIST by electrophoretic base pair (bp) size match to sequenced alleles, Next Generation Sequencing (NGS), and the concordance of results from all commercially available PCR multiplex STR-typing kits of forensic interest at the time of issue.
- **SRM 2971 24R,25-Dihydroxyvitamin D₃ Calibration Solution**⁹⁸
This SRM is intended as a primary calibrant for instruments and techniques used to determine 24R,25(OH)₂D₃. The mass fraction of 24R,25(OH)₂D₃ was value assigned by gravimetric preparation using materials of defined purity and measurement results from an ID-LC-MS/MS RMP.
- **SRM 3949 Folate Vitamers in Frozen Human Serum**^{99,100,101}
This SRM is intended for use in validating methods for determining folate vitamers in human serum. Folic acid, also called vitamin B₉, is used to treat anemia caused by folate deficiency and as a supplement by women during pregnancy to reduce the risk of neural tube defects in the baby.¹⁰² A unit of SRM 3949 consists of three vials each having different levels of the vitamers: low, medium, and high. Folic acid concentrations in the three sera were certified using NIST results from two suitably independent ID-LC-MS/MS methods and ID-LC-MS/MS results provided by the Centers for Disease Control and Prevention (CDC).

3.3. One Reference Measurement Procedure at NIST and Expert Collaborators or Interlaboratory Studies (ILS)

Value-assignment based on NIST results from one well-characterized RMP (not necessarily a higher-order RMP) combined with results from:

- one or more expert collaborating laboratories using well-characterized RMPs substantially different from the RMP used by NIST. Reporting requirements for the expert collaborators' results are specified in the certification plan. The collaborators' report contains enough detail about the method, calibrants, and control materials to permit NIST to evaluate the fitness of the measurements.
- a suitably large ILS documented and administered by NIST or an experienced organization in collaboration with NIST. Results from the study are provided with enough detail to enable independent assessment of the consensus value.

This mode is appropriate when NIST has implemented and critically evaluated one suitable RMP for the measurand and there are suitable expert collaborators that can supply results from independent RMPs or consensus results from one or more suitably large ILSs. Examples include:

- **SRM 968f Fat-Soluble Vitamins in Frozen Human Serum**¹⁰³
This SRM is intended for validating methods for determining fat-soluble vitamins in human serum and plasma and for qualifying control materials produced in-house and analyzed using those methods. Values for three fat-soluble vitamins were certified from NIST results provided by a well-characterized and validated liquid chromatographic RMP and from three NIST-coordinated ILSs, each with more than 20 participants.
- **SRM 1635a Trace Elements in Coal (Subbituminous)**¹⁰⁴
This SRM is intended for the evaluation of techniques used in the analysis of coals and materials of a similar matrix. The certified mass fraction value for sulfur is based on measurements made at NIST using microwave-induced combustion and isotope dilution via sector-field inductively coupled plasma mass spectrometry (ICP-MS) and results from several published RMPs provided by participants in the CANSPEX 2008–3 ILS, conducted by Quality Associates International, Ltd.
- **SRM 2034 Holmium Oxide Solution Wavelength Standard (240 nm to 650 nm)**^{105,106,107}
This SRM is a transfer standard intended for the verification and calibration of the wavelength scale of ultraviolet and visible absorption spectrophotometers having nominal spectral bandwidths not exceeding 3 nm. The locations of transmittance minima for 14 absorption bands of a holmium oxide solution, containing a mass concentration of 40 g/L in 10 % (volume fraction) perchloric acid in distilled water, were certified using primary ratio results from multiple determinations by 15 independently calibrated research spectrophotometers. While these measurements were for a single preparation of the solution, they were coupled with comparisons of many preparations of the material evaluated on a single instrument at NIST.
- **SRM 2894 Ethanol-Water Solution (Nominal Mass Fraction 0.1 %)**¹⁰⁸
SRM 2894 is intended for use in the calibration of instruments and techniques used for the determination of ethanol in blood. The mass fractions of ethanol in water in this and several related SRMs were certified based on gravimetric preparation and purity measurements made at NIST, titrimetric determinations made at the National Measurement Institute of South Africa, and exact matching isotope dilution-gas chromatographic/mass spectrometry (ID-GC/MS) measurements made at the National Metrology Institute of Australia.
- **SRM 3280 Multivitamin/Multielement Tablets**^{109,110}
SRM 3280 is intended to be used in validating analytical methods for the determination of vitamins, carotenoids, and elements in dietary supplement tablets. The SRM is provided as whole tablets because some of the vitamins are encapsulated to provide stability, and grinding would

compromise this coating. Value assignments were based on the combined measurements from several different RMPs at NIST and the U.S. Department of Agriculture (USDA), results from an ILS organized by the Grocery Manufacturers Association Food Industry Analytical Chemists Committee (GMA FIACC), and an ILS organized by the European Committee for Standardization (CEN).

3.4. Value Transfer from an Existing Standard Reference Material or Primary Standard

Value assignment for individual measurands can be based on the calibration of a NIST-characterized RMP using a closely matched existing SRM. This is appropriate when preparing a new issue of an existing CRM.

- **Gas NTRMs**^{18,19}

A gas NTRM can be developed for any pollutant, concentration, and balance gas combination for which a PS, SRM, and measurement procedure exist. Batches of NTRM gas cylinders are produced by qualified specialty gas providers. The producer monitors the entire batch of cylinders for homogeneity and stability and, if they deem the batch [fit-for-purpose](#), provides NIST with the data. NIST reviews the data and selects a subset of the batch for analysis at NIST. If the data are considered fit-for-purpose, NIST value-assigns the batch.

- **SRM 1761a Low Alloy Steel**¹¹¹

This and related SRMs are intended for the evaluation and calibration of instrumental methods of analysis used by the ferrous metals industry. The measurement precision provided by modern X-ray fluorescence (XRF) wavelength dispersive spectrometers enables transfer of elemental composition values from an existing SRM to a new version of similar composition. Transfer is accomplished using calibration standards and enough samples of original and renewal materials to demonstrate the homogeneity of each. Matrix corrections are insignificant when the base matrix mass fractions differ by no more than a few percent and the measurand mass fractions agree within about 10 % or are low enough to guarantee that a linear calibration model adequately represents the response. Calibration of the XRF spectrometer and measurement of SRM 1761 samples ensure that:

- the measurement procedure is under control,
- the linear calibration model performs as required, and
- all SRMs of the chosen type correlate well in the available mass fraction ranges.

The SRM 1761a certified values are traceable to the PSs and calibrations used to certify the values delivered by SRM 1761.

3.5. Operationally Defined Measurands

[ISO 17034:2016:3.7] describes an operationally defined measurand as a “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.” For these measurands, certification is based on results from the appropriate and validated use of the procedure. Measurement results are obtained by NIST or a collaborator with practical experience using the procedure. The reporting requirements for the collaborators are specified in the certification plan with their reports containing enough detail to permit NIST to evaluate the fitness of the measurements.

Since the “true value” for an operationally defined measurand is the result provided by the procedure, the measurement uncertainty associated with the result combines the procedure’s reproducibility imprecision, uncertainty in instrumental bias corrections, and material heterogeneity and instability. Certified values are metrologically traceable to the measurement procedure, which in the case of an operationally defined measurand is the higher-order reference system for that measurand.

This mode is appropriate when:

- the measurand is uniquely defined by the procedure,
- the procedure is well-documented, typically by a standards organization or government agency, and
- the procedure is widely known, accepted, and used by the relevant measurement communities.

Selected current examples are:

- **SRM 185i Potassium Hydrogen Phthalate pH Standard**^{112,113}
This NIST pH SRM is intended for use in preparing solutions for calibrating pH electrodes. The SRM is a high-purity solid that delivers a pH buffer having a nominal standard pH value of 4 for 0.05 mol/kg solutions prepared according to a specified protocol. Standard pH values are assigned for this buffer using the primary direct RMP based on the Harned cell and the conventional value for the single-ion activity coefficient of the chloride ion. The RMP is periodically validated through ILS comparisons with other [peer organizations](#). Material homogeneity is assessed using glass electrode measurements, with previous issues of the SRM analyzed as controls.
- **SRM 2812 Rockwell C Scale Hardness – High Range**^{114,115}
SRM 2812 is a transfer standard intended for use in calibration and verification of the performance of Rockwell hardness equipment using the Rockwell C Hardness Scale (HRC), an empirical indentation hardness test that can provide useful information about metallic materials. Each individually certified unit of SRM 2812 is a 64 mm diameter and 15 mm thick steel test block. Hardness is measured by indentation tests in accordance with the Rockwell hardness principle defined by the CIPM's Consultative Committee for Mass and Related Quantities (CCM) Working Group on Hardness using the NIST standardizing hardness tester and diamond indenter, as described in the SRM Certificate. The tester is a specially designed measuring instrument using directly loaded dead-weights for applying the required forces, and a laser interferometry displacement sensor for measuring the depth of indentation. The geometry of the NIST standardizing diamond indenter was verified using a stylus instrument.
- **SRM 2092 Low- Energy, SRM 2096 High-Energy, and SRM 2098 Super-High-Energy V-Notch Specimens (NIST-Verification, 8-mm Striker)**^{116,117,118,119,120}
These SRMs are intended for the verification of Charpy impact machines equipped with an 8-mm striker. Each unit consists of a set of alloy steel notched bars needed to perform a single machine verification. The bars have been finished to length, heat-treated, and machined to provide a certified absorbed energy within the ranges (13 J to 20 J, 88 J to 136 J, 176 J to 244 J). A Machine Verification Letter and Sticker are provided to the user's facility upon receipt of the fractured specimens and completed questionnaire. This Verification Letter provides the certified values and their associated uncertainties. Depending on which standard is employed, the customer's result is traceable to international standards ASTM E23 - Notched Bar Impact Testing of Metallic Materials or ISO 148-2:2016 Metallic materials - Charpy pendulum impact test - Part 2: Verification of testing machines.
- **Proximates in SRM 1869 Infant/Adult Nutritional Formula II (milk/whey/soy-based)**¹²¹
This SRM is intended for validation of methods for determining proximates and other measurands in infant and adult nutritional formulas and similar materials. Certified mass fraction values for solids, ash, and protein are based on measurements made by LACOMET, Costa Rica's national metrology institute, and participants in a NIST-organized ILS involving more than 60 participants from the food and infant formula industries. The assigned values are metrologically traceable to Official Methods of Analysis established by AOAC International.

- **SRM 1898 Titanium Dioxide Nanomaterial** ^{122,123}

This SRM is intended as a benchmark and investigative tool for evaluation of the potential environmental, health, and safety risks associated with manufactured nanomaterials. A unit consists of 15 g of mixed anatase and rutile nanocrystalline titanium dioxide (TiO₂) in the form of a dry agglomerated powder. Single-point and multi-point Brunauer-Emmet-Teller (BET) specific surface area measurements used to establish certified values were obtained using commercial gas sorption instruments at NIST and at three expert collaborating laboratories using a defined method based on a static, volumetric technique traceable to ISO 9277:2010 *Determination of the specific surface area of solids by gas adsorption — BET method*. The values were validated with results from a 20-participant ILS.

3.6. Values Defined by International Convention

NIST supplies a number of special-purpose international primary measurement standards that are defined by artifact materials value-assigned by international convention rather than measurement. These materials define the zero or span for various isotopic “ δ -scales” used to unambiguously express small differences in isotope amount or number ratios in the same manner that the International Prototype of the Kilogram ¹²⁴ defined the kilogram from 1889 to 2019. The values delivered by these δ -scale “anchor” materials are intrinsically absolute without uncertainty.

These materials have historically been provided as NIST RMs. It is intended that by recognizing their special role in defining higher-order reference systems (i.e., the internationally recognized δ scales), to which metrological traceability for isotope ratio measurement values can be established, they can become NIST SRMs. Examples include:

- **Reference Material 8537 Standard Light Antarctic Precipitation (Water)** ¹²⁵

This RM, known colloquially as SLAP, anchors the deuterium-depleted end of the $\delta^2\text{H}_{\text{VSMOW-SLAP}}$ scale, where VSMOW stands for Vienna Standard Mean Ocean Water, an RM that defines the zero point of the scale. Each unit of the RM consists of 20 mL water in a sealed glass ampoule. Note: This RM is no longer readily available but is realized by a second-generation RM produced to be extremely similar, VSMOW2 (NIST RM 8535a).

- **Reference Material 8554 IAEA-S-1 (Sulfur Isotopes in Silver Sulfide)** ¹²⁶

This RM defines the Vienna Cañon Diablo Troilite (VCDT) scale for relative differences in sulfur (S) isotope-number ratios, $R(^{34}\text{S}/^{32}\text{S})$. Each unit of the RM consists of one bottle containing approximately 0.5 g of silver sulfide (Ag₂S).

3.7. Need-Driven Exceptions

When a certified value is required, but the above approaches are not appropriate, new metrologically defensible modes are defined. Such exceptional circumstances occur when:

- NIST cannot by itself provide the service in a timely manner, for instance when:
 - analytical procedures need to be developed and validated in concert with producing the material.
 - NIST does not have the specialized expertise, instrumentation, facilities, or regulatory permission needed to establish a critical link in the traceability chain, nor can these be acquired sufficiently quickly.
- Expert collaborators having needed capabilities are available and willing to participate in certification.
- NIST has the expertise to understand the participating organizations’ processes and to evaluate the quality of all provided information (as required by [ISO 17034:2016:6.2]).
- NIST has the expertise to interpret the results.

Under such circumstances, NIST may elect to use the special capabilities or facilities of the expert collaborators to perform laboratory measurements according to NIST-specified designs.

The following illustrate previously encountered challenges and the specialized approaches developed to meet them. Different needs will doubtless arise in the future and require similar inventiveness.

3.7.1. Analytical Development

SRM 2855 Additive Elements in Polyethylene is intended for the calibration or evaluation of methods for elemental analysis of polymers. It was developed in collaboration with ASTM International subcommittee D20.70 at a time during which NIST had no RMP for elements in thermoplastics.^{127,128} Suitable analytical procedures had to be developed and validated at the same time as the materials were being evaluated in an ILS.

- *Challenge:* At the outset of the project, there were no NIST RMPs for elements in polyethylene.
- *Certification procedures:* NIST staff developed XRF and ICP-OES measurement procedures for the specific matrix.
- *Verification procedure:* A commercial set of polyethylene reference materials was used for quality assurance for both NIST RMPs and participant methods. Participants in the ILS reported results using XRF, ICP-OES, and neutron activation analysis.
- *Conclusion:* The NIST results agreed well with the ILS consensus summaries, validating that the NIST RMPs were [fit-for-purpose](#). Certified values were assigned based on the NIST ICP-OES and XRF results combined with the consensus results from the ILS.

3.7.2. Expertise

SRM 3246 *Ginkgo biloba* (Leaves)¹²⁹ is intended for use in validating analytical methods for the determination of flavonoids, terpenes, lactones, and toxic elements in botanical matrices.

- *Challenge:* NIST did not have the taxonomic expertise to identify botanical tissue, hence it did not itself have the equivalent of a higher-order RMP for establishing botanical identity.
- *Certification procedure:* The leaf material used to prepare SRM 3246 was acquired from a commercial source. The identity and uniform composition of this material was confirmed through morphological examination by a credentialed specialist.
- *Verification procedure:* DNA analysis of two characteristic chloroplast sequences was used to verify identity. Sequences from the SRM material were compared to multiple *Ginkgo biloba* voucher specimens (inclusivity panel) and individual voucher specimens or literature sequences of close relatives (exclusivity panel). Confidence in the identification reflects sequence uniformity within the sequences from multiple samples, complete compatibility with the inclusivity panel sequences, and incompatibility with the exclusivity panel sequences. Sequence analysis of multiple samples established genetic uniformity and absence of DNA-containing tissue from common botanical contaminants. (Note: A botanical voucher is “a representative sample of an expertly identified organism that is deposited and stored at a facility from which researchers may later obtain the specimen for examination and further study.”¹³⁰)
- *Conclusion:* Botanical identity was established with the highest confidence through due diligence in acquisition and verification of the source material. Metrological traceability was provided to the *Ginkgo biloba* holotype through the established, internationally recognized voucher system. The approach used was considered to be validated for this particular application.

3.7.3. Instrumentation

SRM 3121 Gold (Au) Standard Solution¹³¹ is intended for use as a primary calibration standard for the quantitative determination of gold. Production of this SRM required assessment of the purity of the metallic gold PS used to prepare calibration solutions for the ICP-OES method. Determining impurities

in metals requires the use of glow discharge mass spectrometry (GDMS); determining the nonmetallic element content of these materials requires inert gas fusion (IGF) and combustion analysis. These three RMPs are internationally recognized as higher-order procedures for assaying impurities in metal samples.

- *Challenge:* While NIST staff had the expertise required, NIST did not have at the time the needed GDMS, IGF, or combustion instrumentation.
- *Certification procedure:* Two sets of GDMS, IGF, and combustion measurements were sourced from expert collaborators. National Research Council Canada (NRCC) and Evans Analytical Group (Liverpool, NY) provided GDMS results. Luvak Laboratories, Inc. (Boylston, MA) provided IGF and combustion analysis results. The purity of the PS was calculated from the combined results at NIST using a NIST-developed, mass-balance purity assessment approach.
- *Verification procedure:* Solutions prepared using SRM 3121 were compared to those prepared from archived materials using ICP-OES measurements.
- *Conclusion:* The certified measurement uncertainty includes components for each of the methods, differences between the two sets of GDMS measurements, an allowance for nondetectable elements, and sample heterogeneity. Metrological traceability is to the SI through the calibration materials used in the analyses. Owing to the verification procedure and a thorough theoretical assessment, the approach was considered validated.

3.7.4. Facilities and Permission

SRM 1877 Beryllium Oxide Powder^{132,133} is intended for use in laboratory analysis and health research for the development and validation of analytical methods and instruments used to determine beryllium, supporting the industries that produce high-performance alloys and ceramics. Beryllium oxide (BeO) powder is toxic, and the very fine powder is difficult to confine.

- *Challenge:* While NIST has the expertise and a higher-order RMP (exact matching ICP-OES) for evaluating the mass fraction of beryllium in solution, it does not have the facilities or required Occupational Health and Safety Administration (OSHA) regulatory approval to work with or package the BeO powder.¹³⁴
- *Certification procedure:* Sets of solutions for ICP-OES analysis were prepared by expert collaborators who had the experience, equipment, and regulatory approval needed to work with the powder safely. Each collaborator utilized a unique digestion protocol. After preparation, the solutions were shipped to NIST for analyses.
- *Verification procedure:* NIST provided the collaborating laboratories with the packaged BeO powder, solution preparation protocols, and balance quality assurance kits. Collaborators were asked to confirm the calibration of their balances before they prepared their solutions.
- *Conclusion:* The collaborating laboratories provided NIST with four independently prepared Be solutions. The NIST RMP results for these solutions agreed within 0.074 %, confirming the homogeneity of the material and its fitness for use by the target industries. Given the strong independence in the solution preparations, the results validated the approach for this application.

3.7.5. Stability and Reassessment

SRM 972a Vitamin D Metabolites in Frozen Human Serum^{135,136} is intended for use as an accuracy control in the critical evaluation of methods for determining the amount-of-substance concentration of vitamin D metabolites in human serum. The determination of individual vitamin D metabolites required a liquid chromatography-mass spectrometry (LC-MS) procedure and a liquid chromatography-tandem mass spectrometry (LC-MS/MS) RMP at NIST and an LC-MS/MS RMP at the CDC. Several years after the initial certification, the CDC indicated that their refined LC-MS/MS RMP was resulting in 25(OH)D₂ values for SRM 972a Level 3 which were slightly outside the certified range.

- *Challenge:* While NIST staff had the expertise required to perform measurements, staff and instrumentation were not available to run additional SRM 972a samples for stability check and possible reassessment of the 25(OH)D₂ certified values in a timely manner.
- *Certification procedure:* NIST combined the original certified values for 25(OH)D₂ with control values for SRM 972a reported by both the CDC and NIST during recent vitamin D metabolite measurement campaigns. The updated certified values for 25(OH)D₂ for Level 2 and Level 3 are consensus means obtained using the Bayesian hierarchical model in the NIST Consensus Builder¹³⁷ on the results from analyses at NIST using ID-LC-MS and ID LC MS/MS and from CDC using two ID-LC-MS/MS procedures.
- *Verification procedure:* All new CDC LC-MS/MS RMP 25(OH)D₂ values for Level 3 were calibrated with NIST SRM 2972a 25-Hydroxyvitamin D Calibration Solutions utilizing Level 2 for quality assurance and passing internal QC parameters. All new NIST LC-MS/MS RMP 25(OH)D₂ values for Level 3 were calibrated with NIST SRM 2972a 25-Hydroxyvitamin D Calibration Solutions or calibration stocks prepared from neat powder with purity determined in-house at NIST by ¹H-qNMR.
- *Conclusion:* NIST leveraged the most recent knowledge from both in-house measurements and an expert collaborator to update the certified values for 25(OH)D₂. The measurement uncertainties include components from the original certified values, the new CDC LC-MS/MS RMP values, and the new NIST LC-MS/MS RMP values. Metrological traceability is to the SI through the calibration materials used in the analyses.

3.8. Recertification

Some SRMs in areas such as optical properties and gas concentrations may be returned to NIST for recertification and extension of their period of validity. This applies only to SRMs that are periodically produced in small quantities, typically with units that are individually certified.

- The Optical Property SRM series (930, 1930, 2031, and 2930) may be recertified for a two-year period of validity. Recertification involves cleaning as well as redetermining and validating the SRM's originally certified properties.
- Gas cylinder SRMs may be re-certified for a defined period of validity upon request, depending on the pressure of the certified gas remaining in the cylinder.

3.9. Non-Certified Values

Any measurement process that provides a defensible [fit-for-purpose](#) estimate of a measurand value can be used to assign a non-certified value.

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