Supelco®
Analytical Products

MERCK

How to choose the correct reference material quality grade for your needs

Quality grades, certificates of analysis, and metrological traceability and what they mean for you

Who uses reference materials?

Reference materials are a critical component of the analytical testing workflow. Through calibration of measurement systems, validation of methods, and quality control programs, reference materials ensure accuracy in testing. From certified reference materials (CRMs) and other quality grades of reference materials, to certificates of analysis, metrological traceability and other concepts, the world of reference materials is vast, and at times, confusing.

These charts present critical reference material topics, offering information on metrological traceability, the hierarchy of reference materials, certificates of analysis, reference material formats and uses, and fit-for-purpose selection considerations. Proper selection of the right reference material for the laboratory's testing application is important, because results are only as accurate as your reference.

Metrological traceability and SI Units of your reference materials

Metrological traceability is an important concept in the world of reference materials. A fundamental term in metrological traceability is the SI unit of measurement. The International System of Units, or SI, defines the seven units of measure as the basic set from which all other SI units can be derived. The two most common SI units of measure for traceability of reference materials are kilogram and mole.

Metrological traceability means measurements can be meaningfully compared, across difference places, at different times, by different people, using different equipment. The measurement result must be related to a reference through a documented and unbroken chain of calibrations, tracing back to the SI unit of measurement.

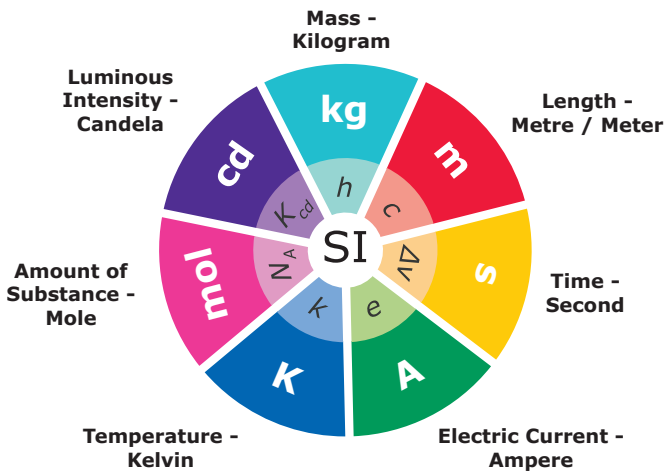
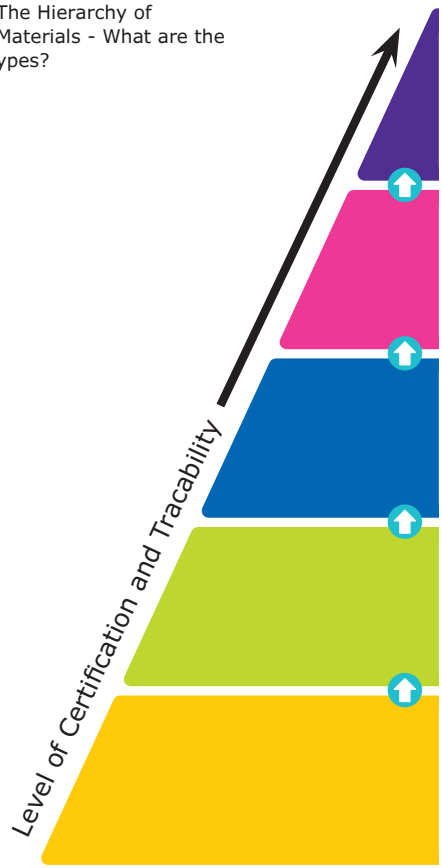


Figure 1. Metrological Traceability – SI Unit of Measurement

ISO 17034 and quality grades of standards, reference materials and certified reference materials

Figure 2. The Hierarchy of Reference Materials - What are the Different Types?



National Metrology Standard (e.g. NIST, JRC, NMI Australia)
Compendial Standard (e.g. USP, EP, BP, JP, IP)
- Issued by an authorized body
- Considered to provide the highest level of accuracy & traceability

Certified Reference Material (CRM) (ISO 17034, 17025)
- Considered to provide the highest level of accuracy, uncertainty, and traceability to an SI unit of measurement
- Manufactured by an accredited Reference Material Producer

Reference Material (RM) (ISO 17034)
- Fulfilling ISO requirements which are less demanding than for CRMs
- Manufactured by an accredited Reference Material Producer

Analytical Standard (ISO 9001)
- Certificate of Analysis available
- Level of certification varies

Reagent Grade / Research Chemical
- May come with a Certificate of Analysis
- Are not characterised for use as reference materials

The reference material hierarchy includes five major quality grades, from national metrology and other primary standards to Certified Reference Materials (CRMs), Reference Materials (RMs), Analytical Standards, and research grade or research chemicals. Level of certification and traceability requirements increase for each higher level. Where national governments give standardization to the top level, specific ISO guidelines provide standardization for CRMs and RMs. These ISO requirements include ISO 17034, ISO/IEC 17025 and ISO Guide 31.

Reference material producers must meet these ISO requirements to manufacture CRMs or RMs. For both of these quality grades, Certificates of Analysis must be provided, and the information contained within is defined by the aforementioned ISO guidelines. The quality specifications for the last two levels are defined by each individual producer rather than by a national government or ISO accreditations specific to CRMs and RMs.

What is measured in each grade of reference material?

Purity and Identity of the material are typically included in the Certificate of Analysis for each of the five quality grades. Content and Stability are required for the primary standards or ISO-defined CRM and RM.

Analytical standards and research chemicals may or may not include these two parameters as their inclusion is dependent on the producer. Analytical Standards can also in some cases be Quality Control materials compliant with ISO Guide 80.

Homogeneity is required for the primary standards, CRM, and RM, but this parameter will not be found with the lower quality grades. Uncertainty and Traceability information are limited to just the primary standards and CRM. In the pharmaceutical world, secondary standards can be CRMs or RMs, but here, there are two different types of traceability – to the SI unit of measurement for the ISO-defined CRM as well as traceability to the primary compendial standard, which is a requirement specific to pharmaceutical secondary standards.

Parameter	NMI Standard	Compendial Standard	CRM	RM	Analytical Standard	Research Chemical
Purity	✔	✔	✔	✔	✔	✔
Identity	✔	✔	✔	✔	✔	✔
Content	✔	✔	✔	✔	maybe	
Stability	✔	✔	✔	✔	✔	
Homogeneity	✔	✔	✔	✔		
Uncertainty	✔		✔			
Traceability	✔		✔	✔		
Type	Primary Measurement Standard or Primary Standard (Pharma)		Primary or Secondary Standard (Pharma)	Secondary Standard (Pharma)		

Table 1. The Hierarchy of Reference Materials – What's the Difference?

Understanding your reference material Certificate of Analysis

With the Certified Reference Material (CRM) or Reference Material grade comes the Certificate of Analysis (CoA). Within the CoA, there are several quality parameters which are critical to understand: accuracy, consistency, homogeneity, purity, and stability. Also, what is being certified is important to understand – namely, the certified property value, whether a concentration, potency or content.

Be sure to examine the CoA for the producer's quality systems, the reference material's certification process, and supporting information on traceability for a CRM. The CoA is important since it can give the laboratory information which ensures the reference material's certification is fit for purpose within the testing method or application.

Supelco®

www.sigmaaldrich.com

Certificate of Analysis – Certified Reference Material

Gold standard for ICP

TraceCERT®

Product no.:	38168
Lot no.:	Sample
Description of CRM:	Gold metal (high-purity quality) in 5% HCl (prepared with HCl suitable for trace analysis and high-purity water, 18.2 MΩ.cm, 0.22 µm filtered).
Expiry date:	NOV 2020
Storage:	5-30°C
Density (certified) at 20°C:	1024.2 kg m^{-3} ± 0.5 kg m^{-3}

Constituent	Certified values at 20°C and expanded uncertainties, U = *k* .u (*k* = 2) [1][2]	
Gold	**976 mg kg^{-1} ± 2 mg kg^{-1}**	**1'000 mg L^{-1} ± 2 mg L^{-1}**

Metrological traceability:	Certified values are traceable to the International System of units (SI) through a metrologically valid weighing process. Details see "Details on metrological traceability". [3]
Measurement method:	The certified value is determined by high-precision weighing of thoroughly characterized starting materials and verified by measurement against NIST SRMs or similar CRMs
Intended use:	Calibration of ICP, AAS, spectrophotometry or any other analytical technique.
Instructions for handling and correct use:	This reference material shall be stored in the original closed bag between 5°C and 30°C. Before every use of the material the bottle must be shaken well and its temperature has to be 20°C. If storage of a partially used bottle is necessary, the cap should be tightly sealed and the bottle should be stored at reduced temperature (e.g. refrigerator) to minimize transpiration rate. We highly recommend using this reference material no longer than 15 months after the aluminum bag was opened.
Health and safety information:	Please refer to the Safety Data Sheet for detailed information about the nature of any hazard and appropriate precautions to be taken.
Accreditation:	Sigma-Aldrich Production GmbH is accredited by the Swiss accreditation authority SAS as registered reference material producer SRMS 0001 in accordance with ISO 17034 and registered testing laboratory STS 0490 according to ISO/IEC 17025. [4][5]
Certificate issue date:	04 APR 2019
Packaging:	100 mL HDPE bottle sealed with an aluminized bag

ISO 17034 SRMS 0001 | ISO/IEC 17025 STS 0490 | ISO 9001 005356 QM08

S. Matt – CRM Operations

Dr. P. Zell – Approving Officer

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Sigma-Aldrich Production GmbH is a subsidiary of Merck KGaA, Darmstadt, Germany.

Accuracy
Comparison to a primary source or certified second source – curve/ calibration standard. Comparison of multiple independent preparations.

Consistency
Lot-to-lot consistency verified by comparing to the previous lot.

Stability
Expiration date established though real-time stability studies.

Homogeneity
Across the batch of ampoules/vials.

Purity
Consistent with the neat material. No contamination or degradation.

Reference Material Formats – Do you need a neat, solution, or matrix material?

Reference materials can be used in different formats in the testing laboratory, depending on product availability and method requirements. The three formats for reference materials are a neat or powder form, in solution, or matrix. The Supelco® family of reference materials includes CRMs, RMs, or Analytical Standards in each format depending on the testing laboratory's need and testing application.

	Neat Analyte	In Solution	In Matrix
Form	Vial/Lyophilized	Ampoules/Vials/Bottles	Ampoules/Vials/Bottles
Uses	Weigh daily/weekly to make stock levels & working solutions	Ready-made, certified and ready to use or dilute	Ready-made and certified at working level in matrix of choice
Pros	Widely available	Convenient - Saves time	Convenient - Saves time
	Flexible to use in a variety of applications	Concentration is certified & traceable	Remove need to further dilute into matrix of choice
	Larger unit sizes available	Stable - protected from evaporation, transpiration, O_2	Concentration and stability is certified and traceable
Cons	May be hard to handle: Hygroscopic, viscous, unstable	Need correct mix of analytes at right concentration and volumes	Long-term analyte stability in matrix vs. diluent
	Time consuming	Diluent compatibility with method	Special handling considerations & storage of biological matrices
	Potentially greater week-week variability in results		

Table 2. Different Formats – How Reference Materials are Used in the Testing Laboratory

Choose the correct reference material for your testing purpose

For instrument qualifications and calibrations, establishing and maintaining traceability is critical. The selected reference material should help the laboratory achieve this. In daily routine system suitability applications, it might be important to qualify something that is practical and easy to use, yet reliable and cost effective for everyday use. In method validation, it's critical to use highly accurate and precise materials to show that the laboratory method is accurate and precise. For identity and screening purposes, important attributes of reference materials include proven authenticity and identity. For quantitation, assays, or stability assessment, stable and accurate reference materials are needed.

Type of test	Use of Ref. Mat.	Examples	Requirements of the Ref. Mat.
Instrument qualification / Calibration	Establish system performance	Annual qualifications	Traceable
	Measurement accuracy	Routine balance calibrations	
Routine calibration / System suitability	Daily / weekly	Pre-use balance calibrations	Qualify as suitable for use
	System / method specific	System performance checks for LC-UV/MS; GC-FID…	
	Establish routine performance		
Method validation	Accuracy	Pharma QC; Environmental testing	Accurate
	Precision	Standards of the analyte(s), interferences, impurities	Traceable
	Specificity & interferences		
	LOD/LOQ & Linearity		
Identity	Comparison of unknown to known	Incoming raw materials in pharma, food etc.	Authenticity
		Screening tests	
Content or assay	Quantitation of analytes	Pesticide/toxin limits	Certified content
		Pharma QC - API content	Traceable
Stability assessment	Monitor product stability	Pharma QC	Stable, homogenous
Internal Quality Control	Method accuracy	Routine quantitation of analytes - pharma/pesticides/diagnostics	Certified content
			Traceable

Table 3. Use of Reference Materials – Type of Test

Which quality grade is the best fit for purpose?

Fit for purpose decisions in selection of reference materials can depend on several factors, from regulatory requirements, availability, and type of testing application to level of accuracy and sample matrix.

Type of Test	NMI Standard	Compendial Standard	CRM	RM	Analytical Standard	Reagent Chemical	Attribute
Instrument qualification / Calibration	✔	✔	✔				Traceability & Accuracy
Routine calibration/ System suitability	✔	✔	✔	✔	maybe		Qualified standard (Primary or secondary)
Method validation	✔	✔	✔	✔			Accuracy, Precision, Bias
Identity	✔	✔	✔	✔	✔	✔	Authenticity
Content or assay	✔	✔	✔	✔	maybe		Qualified standard
Stability assessment	✔	✔	✔	✔	maybe		Qualified standard
Internal Quality Control	✔	✔	✔	✔	maybe		Qualified standard
Regulatory / Accreditation	✔	✔	✔	✔			Qualified standard

Table 4. Fit for Purpose Guidance in Standard Selection

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