

P102a - Policy on Reference Material Traceability for Life Sciences Testing Laboratories

Introduction

The Life Sciences Advisory Committee realizes that the traceability of reference standards and reference materials (RMs) per the requirements of ISO/IEC 17025:2005, Section 5.6.3 may be challenging for laboratories to apply in certain circumstances. This document explains how biological, drug, and chemical materials are expected to be processed, and how they can be used within life sciences laboratories to meet traceability requirements.

To assist the reader in understanding the approach, this document describes four categories of reference materials. All of these categories are considered to demonstrate traceability, but the level of traceability depends on the use of the material. The laboratory is required to provide evidence showing that traceability has been evaluated and appropriately established, including records documenting the evaluations. However these examples are not all inclusive. In cases where a laboratory makes their own Reference materials the laboratory must comply with ISO Guides 34 and/or ISO 17511:2003 [*In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials*].

Establishing metrological traceability to SI units may not be possible in all areas of life sciences. This issue has been addressed in detail in a number of documents including ISO 17511. To quote ISO 17511:

“In many cases, at present, there is no metrological traceability above the manufacturer's selected measurement procedure or the manufacturer's working calibrator. In such cases, trueness is referred to that level of the calibration hierarchy until an internationally agreed reference measurement procedure and/or calibrator becomes available.”

To ensure consistent interpretation by laboratories and A2LA assessors within A2LA Life Sciences Laboratories, the following definitions and guidelines apply:

Definition of Terms

Reference material (ISO Guide 35:2006): Material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process. Note: Generally these materials are considered to be “consumable”.

Reference method (ISO Guide 30:1992): Thoroughly investigated method, clearly and exactly describing the necessary conditions and procedures, for the measurement for one or more property values that has been shown to have accuracy and precision commensurate with its intended use and that can therefore be used to assess the accuracy of other methods for the same measurement, particularly in permitting the characterization of an RM.

Reference standard (ISO Guide 30:1992): standard, generally having the highest metrological quality available at a given location or in a given organization, from which measurements made there are derived.

Certified Reference Material (ISO Guide 35:2006): reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that

provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability.

Traceability: (ISO Guide 30:1992 and ISO Guide 34:2000, section 5.12.2): satisfactory evidence of the correlation of results with other stated values either by exhaustive evaluation of the measurement process or by correlation with known and accepted national and/or international certified reference materials NMI, also property of the result of a measurement or the value of a standard whereby it can be related, with a stated uncertainty, to stated references, usually national or international standards, through an unbroken chain of comparisons.

Process Description

Four categories of traceability have been defined for use in Life Sciences. The use of a material in a measurement process determines the appropriate category of reference material to be used. Category I materials are traceable to a national metrology institute (NMI), reference material provider (RMP) or accredited calibration provider as described in A2LA Traceability Policy (T1). Prior to selection of an RMP, the user may have to determine whether the RMP is compliant to ILAC-G9:2005 (*Guidelines for the Selection and Use of Reference Materials*). If the RMP is not compliant the user may request of the RMP to become compliant with ILAC G-9: 2005 or find a compliant RMP. Categories II through IV are those in which a reference material can be considered as being “fit for its intended use in a measurement process” (as stated in ISO Guide 35) without meeting the requirements of T1. Examples of records demonstrating a material is fit for use include the origin and identity of the material, the concentration where applicable, the dates the material was used and the test results of the usage (e.g. concentration, or counts of the organism).¹

Categorical descriptions

Category I: This category includes those materials which are used to establish traceability. Category I materials are expected to be traceable to a national metrology institute (NMI), an accredited reference material producer (RMP) or an accredited calibration service provider as described in A2LA Traceability Policy clause (T1).

Examples (but not limited to):

- common elements such as metals in standard matrices,
- inorganic compounds such as anions,
- some common organic compounds in standard matrices

For Category I reference materials, the laboratory shall comply with the A2LA Traceability Policy on Traceability of Measurement. The reader is referred to the A2LA website, www.a2la.org for that policy.

Category II: There are circumstances in which the material may not be traceable to a national metrology institute (NMI), an accredited reference material provider (RMP) or accredited calibration provider, but can be obtained from an authoritative source or prepared by a published standard procedure. Because defined *operations* are used to obtain or generate these materials, they can be thought of as exhibiting *operational traceability*.

¹ Note that records of use are not to be confused with backwards chain of custody requirements.

There are cases where traceability is based on customer contract requirements, government regulations, manufacturer's methods, or other external circumstances that require laboratories to employ specific reference materials. When laboratories are required to use such reference materials, identified by authoritative and/or definitive sources, including manufacturer, customer or regulator, these requirements shall be stated, and materials used shall be traceable to those sources.²

Examples (but not limited to):

- Pesticides from repositories
- drug compounds & drug metabolites
- pH buffers, conductivity and water activity standards
- When customer contracts, legal requirements, manufacturer methods or other external requirements specify a Category II material.

In the case of using a Mass Spectrometer (MS) as the detection system, the actual calibration of the MS may be performed by a Category II standard or alternatively by documenting the masses by numerical calculation.

The laboratory is responsible for determining whether Category II materials are appropriate for the intended use and shall maintain records of such determinations, including scientific justification for its use. A validated test procedure must be used to characterize a material as being fit for use. Thus an appropriate level of validation (ISO/IEC 17025 section 5.4.5) *can* be used to support these determinations.

To support the determination that the material is “fit for its purpose” as a reference material, records of the following shall be available:

- Unique identifier or lot number (required)
- Origin (if applicable) (e.g. inorganic, human or animal, vegetable, or microbial),
- Who and where manufactured (may be generated in-house or provided by supplier)
- Issuing authority (e.g. WHO, BCR, IRMM, ChemServ, USP, ATCC)
- Records of characterization (if applicable)
 - molecular form(s) of, or surrogate for the analyte (e.g. steric isomer for an amino acid, or glycerol for glycerol ester),
 - Method used to establish value (AL)
 - matrix (e.g. buffered bovine albumin solution, analyte concentration in water, or soil, analyte concentration in air),
 - state(s) of aggregation (gas, liquid, solid),
 - phase(s) (solution, suspension, lyophilized),
- Records of use (required)

² Note: For example when chemicals are analyzed using material standards to “calibrate” equipment such as a gas or liquid chromatograph, the laboratory can demonstrate traceability through use of a method, a technology or an instrument. (ISO Guide 35, section 9.2, ISO 17511 parts b1 & b4). According to ISO Guide 35, section 9.2 c, in some circumstances, calibration can also be verified by strictly following a fixed recipe (or a defined procedure) to establish a conventional scale.

Category III: There are cases in which life sciences laboratories are required to develop, validate, or use methods for which no Category I or Category II materials are available (i.e., traceability to the SI or to an NMI or to an accredited provider does not exist *and* there are no authoritative sources or published standard preparation procedures available). These cases may arise when unusual reference materials are needed to validate a new method or technology.

Note: ISO 17511 anticipates this possibility. “*When such materials are used for validation or verification purposes, the laboratory can thus demonstrate traceability through “in-house” measurement procedures*” (ISO 17511, Introduction, part b4).

Examples (but not limited to):

- Rare, unusual or specialized materials
- Newly discovered materials
- Materials in unusual matrices
- Older materials of new importance
- Unstable materials
- Materials that are not normally available in the required concentration, purity, mixture, form or matrix needed for the method being developed, validated or used.
- Bioassay analysis for radionuclides
- Terrestrial analysis and testing plants

The laboratory is responsible for determining whether Category III materials are appropriate for the intended use and shall maintain records of such determinations. An appropriate level of validation (e.g., ISO 17025 section 5.4.5.2) *shall* be used to support these determinations.

To support the determination that the material is fit for use as a reference material, records of the following shall be available:

- Unique identifier or lot number (required)
- Origin (if applicable) (e.g. inorganic, human or animal, vegetable, or microbial),
- Who and where manufactured (may be generated in-house or provided by supplier)
- Issuing authority (if applicable) (e.g. WHO, BCR, IRMM, ChemServ, USP, ATCC)
- Records of characterization (if applicable)
 - molecular form(s) of or surrogate for the analyte (e.g. steric isomer for an amino acid, or glycerol for glycerol ester),
 - matrix (e.g. buffered bovine albumin solution),
 - state(s) of aggregation (gas, liquid, solid),
 - phase(s) (solution, suspension, lyophilized),
- Records of use (required)
- Records of Materials Validation activities including an appropriate validation plan, acceptance criteria, and results (as appropriate)

Category IV: Some materials by virtue of their use as **process controls** serve as a reproducibility standard and are not used as a reference material or standard. In this case traceability requirements are satisfied by the ability to demonstrate that the material is fit for its intended use.

Examples may include (but are not limited to):

- Microorganisms
- cells, cell lines, tissues
- viruses
- antibodies
- enzymes
- commercial kit positive controls
- drug compounds & drug metabolites
- Properties of fuels such as cloud point, carbon residue in fuels, many general fuels analysis

Note: Some of these examples also appear in other categories. The key distinction between Category IV and other categories is that these materials are used as measurement or testing process controls and not to establish traceability claims.

To support the demonstration that the material is “fit for its purpose” as a process control, records of the following shall be available:

- Unique identifier or lot number (required)
- Description including (as appropriate):
 - Origin, (e.g. inorganic, human or animal, vegetable, or microbial)
 - Who and where manufactured (may be generated in-house or provided by supplier)
 - Other pertinent information
- Records of use and process control results (required)

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See Appendix A for a full bibliography.

– APPENDIX A –

The following sources were used as the basis for the Policy on Reference Material Traceability for Life Sciences Testing Laboratories:

- [1] ISO/ IEC 17025:2005, General requirements for the competence of testing and calibration laboratories
- [2] ISO 17511:2003, In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials
- [3] ILAC G9:2005, Guidelines for the Selection and Use of Reference Materials
- [4] ISO Guide 30:1992, Terms and definitions used in connection with reference materials
- [5] ISO GUIDE 34:2000, General requirements for the competence of reference material producers
- [6] ISO Guide 35:2006, Certification of reference materials — General and statistical principles
- [7] A2LA Policy on Measurement Traceability, May 2006