Questions and answers for enhancing the understanding metrological traceability

Authored by Elvar Theodorsson (elvar.theodorsson@liu.se, +46736209471) and reviewed by the JCTLM Traceability Education & Promotion Working group and by other beneficiaries of the JCTLM

BIPM in Paris in 2022

This is a "living document", version 2022-03-21. Suggestions for improvements are gratefully received.

JCTLM Secretariat

Bureau International des Poids et Mesures
Pavillon de Breteuil
92312 Sèvres
Cedex France
Tel: +33 1 45 07 70 70
Fax: +33 1 45 34 20 21
Email: jctlm@bipm.org

Questions and answers for enhancing the understanding of metrological traceability

Traceability is superficially a simple concept, but its implications are multidimensional and complex, e.g., captured by Possolo et al. at the NIST (1).

Q1. Do interlaboratory comparisons – external quality assurance (EQA) – proficiency testing (PT) establish traceability?

No – they do not establish traceability of measurement results since they only deliver information a posteriory (2). Traceability of measurement results requires that the results are shown to be linked *vertically* to an independent and common reference through an uninterrupted chain of comparisons before the measurements of the unknown samples are performed. *Horizontal* comparisons between measuring systems do not suffice.

However, interlaboratory comparisons are crucial when investigating to what extent traceability hierarchies to a common reference have succeeded in reducing overall measurement uncertainty and for monitoring the maintenance of traceability of measurement results over time.

Q2. What legitimate traceability claims can be made if a laboratory has used a single non-certified calibrator?

A "single non-certified calibrator" may or may not represent a certified reference material. Suppose an explicit documentation of traceability to a certified value of certified reference material or a result of a reference measurement system is not available. In that case, the single calibrator is not traceable. Furthermore, the single calibrator may or may not fulfill necessary criteria of fitness for the intended use, such as linearity or the absence of proportional bias. Finally, since no information on the uncertainty of a possible traceability chain for the "single non-certified calibrator" is available, the available information is not sufficient for claims of traceability.

Therefore, the conclusion is that no claim of metrological traceability can be based on a "single non-certified calibrator" if reliable information on its traceability and calibration hierarchy uncertainty is not available.

Q3. What legitimate traceability claims can be made if a laboratory has used a single certified reference material for calibration?

A claim of metrological traceability can be based on a single concentration of certified reference material, provided it is shown that a serial dilution of the certified reference material results in a linear calibration function devoid of proportional bias. Furthermore, the fundaments of traceability in laboratory medicine must be present:

1. The measuring systems used by manufacturers and laboratories alike must be f*it for the intended use* through *validation*/verification and appropriate calibration.
2. The measuring principles used must have been proven fit for the intended diagnostic use during both technical- (3, 4)and diagnostic validation (5) to establish that a measuring system fulfills appropriate performance specifications (6-9).
3. The laboratory must have *documented quality management* through basic education and continued education of its staff, documented quality systems, e.g., ISO-17025 or ISO-15189, with regular auditing by relevant authorities. The quality system must include optimal internal- and external quality control schemes.
4. The *external quality assessment* (EQA) should optimally be trueness-based, using commutable- reference value materials.
5. There must also be documented procedures for monitoring and maintaining traceability of all traceable measurands over *time* (10, 11) since reference materials in Laboratory Medicine have varying and limited shelf-life, which influences the timelines of their traceability.

Q4. What legitimate traceability claims can be made if a laboratory has used a single certified reference material for internal quality control?

Traceability is established through a calibration hierarchy only. Internal and external quality control samples or schemes can be used for repeated control of maintained traceability but not for establishing traceability nor the basis for traceability claims.

Q5. Can measuring systems be traceable?

No – only measurement results are traceable.

Q6. Can measurement methods be traceable?

No – only measurement results are traceable.

Q7. Can calibrators or standards be traceable?

No, the calibrators or standards themselves are not traceable, but measurement results in measuring a measurand may be traceable.

Q8. Can an organization such as LGC or NIST be traceable?

No – only measurement results are traceable.

Q9. What documentation is needed for claims of traceability?

A laboratory claiming that a measurement result is traceable must document the measuring system used and describe the hierarchy of calibrations that were used to establish traceability to a specified reference:

1. The measurand must be defined.
2. The measuring system and the calibrators used when performing the measurement must be documented.
3. The measurement result, including its measurement uncertainty, must be reported.
4. Measuring systems used by manufacturers and laboratories alike must be fit for the intended use through validation/verification and appropriate calibration. The measuring principles used must have been proven fit for the intended diagnostic use during both technical- (8, 9) and diagnostic validation (10) to establish that a measuring system fulfills appropriate performance specifications (11-14).
5. The laboratory must have documented quality management through basic education and continued education of its staff, documented quality systems, e.g., ISO-17025 or ISO-15189, with regular auditing by relevant authorities. The quality system must include optimal internal- and external quality control schemes.
6. The external quality assessment (EQA) should, if possible, be trueness-based, using commutable- reference value materials.
7. There must also be documented procedures for monitoring and maintaining traceability of all traceable measurands over time (15, 16) since reference materials in Laboratory Medicine have varying and limited shelf-life, which influences the timelines of their traceability.

Q 10. Who is responsible for assessing the validity of the claims of traceability?

The user of measurement results is responsible for assessing the validity of the claims of traceability. The provider of a measurement result is responsible for providing the information that the user needs for the assessment (12).

Q 11. Does metrological traceability need to be re-examined periodically?

Yes – traceability needs to be reexamined periodically at intervals dependent on several factors (10, 11) including:

1- Client needs or requests.
2- The stability of the measuring system or the reference materials.
3- Environmental effects.

Q12. Should the uncertainty of the traceability hierarchy be added to repeatability and reproducibility measurement uncertainties when making claims of measurement uncertainty?

Yes – the measurement uncertainty of measurements of unknown samples should be estimated by adding the repeatability or reproducibility measurement uncertainty estimated from the internal quality control samples to the measurement uncertainty of the traceability hierarchy.

Q13. Can a legitimate claim of traceability of a measurement result be based on a result corrected by a single measurement of certified reference material?

No – traceability is based on a "documented unbroken chain of calibrations." A single measurement of certified reference material does not fulfill this fundamental criterion. Furthermore, the simple fact that the persons responsible for the measuring system rely on a correction by a single certified reference material indicates a lack of confidence in the essential calibration hierarchy.

Q 14. Can "operationally defined measurands" (measurands calibrated using "international conventional reference materials" be traceable?

Yes – "operationally defined measurands" that cannot be expressed in SI units can be metrologically traceable through internationally agreed-upon *measurement procedures* or the quantity value carried by *certified reference materials,* e.g., international conventional reference materials.

The metrological traceability must be realized through an unbroken hierarchy of calibrations or comparisons. The intact traceability hierarchy ensures that the metrological traceability of a measurement result has been established to a stated metrological reference.

The essential foundation of international conventional reference materials is an international consensus that a particular manufacturer of reference materials, materials from this manufacturer, or a specific measurement procedure should be the core reference material or reference measurement procedure at the top of the traceability hierarchy.

As always, the fundaments of traceability in laboratory medicine must be present for any claim of traceability in Laboratory Medicine:

1. The measuring systems used by manufacturers and laboratories alike must be f*it for the intended use* through *validation*/verification and appropriate calibration.
2. The measuring principles used must have been proven fit for the intended diagnostic use during both technical- (3, 4)and diagnostic validation (5) to

establish that a measuring system fulfills appropriate performance specifications (6-9).

3. The laboratory must have *documented quality management* through basic education and continued education of its staff, documented quality systems, e.g., ISO-17025 or ISO-15189, with regular auditing by relevant authorities. The quality system must include optimal internal- and external quality control schemes.
4. The *external quality assessment* (EQA) should, if possible, be trueness-based, using commutable- reference value materials.
5. There must also be documented procedures for monitoring and maintaining traceability of all traceable measurands over *time* (10, 11) since reference materials in Laboratory Medicine have varying and limited shelf-life, which influences the timelines of their traceability.

Equivalent measurement results in Laboratory Medicine contribute identically to medical decisions and fulfill the criteria for traceability, including the fundamentals of traceability.

Even though measurement results are traceable, they are not necessarily equivalent. Immunochemical measurement methods represent typical examples where antibodies raised against the analyte commonly bind to different epitopes. Different epitopes may result in various medical interpretations of the results.

Q 15. Are immunochemical measurement results traceable to the same WHO international reference material for Thyreotropin (TSH) implicitly equivalent?

No – they are not – because the antibodies used in the immunochemical methods may not necessarily bind to the same epitopes of the TSH. The measurand TSH is essentially a surrogate quantity for the "analyte" TSH. The quantities measured by the two immunochemical measurement methods for TSH are not necessarily equivalent even though they are both traceable to the same WHO international reference material.

In Laboratory Medicine, examples like this are a common reason why traceability to SI is preferable.

Q 16. Is the average value of measurement results of a proficiency testing sample implicitly traceable?

No – it is not. It is not a certified value of reference material, nor the result of a reference measurement method, and not the definition of an SI unit. Furthermore, a measurement hierarchy is not involved. Again – proficiency testing samples do not provide traceability of measurement results since they only deliver information a posteriory (2). Traceability of measurement results requires that the results are shown to be linked

vertically to an independent and common reference through an uninterrupted chain of comparisons before the measurements of the unknown samples are performed. *Horizontal* comparisons between measuring systems do not suffice.

Q 17. What legitimate claims of traceability can be made provided a laboratory has used counting of single nucleotide sequences and a single certified reference material for calibration?

The single reference material used in this instance is not of primary importance. Accurate counting of the specific nucleic acid sequence is a higher-order *reference measurement method* that can be appropriately calibrated using single certified reference material.

Notably, the fundaments of traceability in laboratory medicine must as always be present for claims of traceability:

1. The measuring systems used by manufacturers and laboratories alike must be f*it for the intended use* through *validation*/verification and appropriate calibration.
2. The measuring principles used must have been proven fit for the intended diagnostic use during both technical- (3, 4)and diagnostic validation (5) to establish that a measuring system fulfills appropriate performance specifications (6-9).
3. The laboratory must have *documented quality management* through basic education and continued education of its staff, documented quality systems, e.g., ISO-17025 or ISO-15189, with regular auditing by relevant authorities. The quality system must include optimal internal- and external quality control schemes.
4. The *external quality assessment* (EQA) should, if possible, be trueness-based, using commutable- reference value materials.
5. There must also be documented procedures for monitoring and maintaining traceability of all traceable measurands over *time* (10, 11) since reference materials in Laboratory Medicine have varying and limited shelf-life, which influences the timelines of their traceability.

Q 18. How many certified reference materials are needed to estimate a measuring system's bias?

A single concentration of certified reference material for a measurand is not sufficient for determining the bias of a measuring system except when evidence is provided that a serial dilution of the patient samples and the certified reference material are parallel.

References

1. Possolo A, Bruce SS, Watters RL. Metrological Traceability Frequently Asked Questions and NIST Policy. 2021. Contract No.: NIST Technical Note 2156.

2. De Bievre P. Do interlaboratory comparisons provide traceability? Accredit Qual Assur. 1999;4(8):342-6.

3. Thompson M, Ellison SLR, Wood R. Harmonized guidelines for single-laboratory validation of methods of analysis - (IUPAC technical report). Pure Appl Chem. 2002;74(5):835-55.

4. Eurachem. The Fitness for Purpose of Analytical Methods (2014) https://www.eurachem.org/index.php/publications/guides/mv. Eurachem; 2014.

5. Thedorsson E, Magnuson B. Full method validation in clinical chemistry. Accredit Qual Assur. 2017.

6. Panteghini M, Sandberg S. Defining analytical performance specifications 15 years after the Stockholm conference. Clinical chemistry and laboratory medicine : CCLM / FESCC. 2015;53(6):829-32.

7. Sandberg S, Fraser CG, Horvath AR, Jansen R, Jones G, Oosterhuis W, et al. Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine. Clinical chemistry and laboratory medicine : CCLM / FESCC. 2015;53(6):833-5.

8. Smith AF, Shinkins B, Hall PS, Hulme CT, Messenger MP. Toward a Framework for Outcome-Based Analytical Performance Specifications: A Methodology Review of Indirect Methods for Evaluating the Impact of Measurement Uncertainty on Clinical Outcomes. Clinical chemistry. 2019.

9. Thue G, Sandberg S. Analytical performance specifications based on how clinicians use laboratory tests. Experiences from a post-analytical external quality assessment programme. Clinical chemistry and laboratory medicine : CCLM / FESCC. 2015;53(6):857-62.

10. Ehrlich CD, Rasberry SD. Metrological timelines in traceability. Metrologia. 1997;34(6):503-14.

11. Ehrlich CD, Rasberry SD. Metrological timelines in traceability. Journal of Research of the National Institute of Standards and Technology. 1998;103(1):93-105.

12. NIST. Supplementary Materials related to NIST Policy on Metrological Traceability 2021 [2021-05-31]. Available from: https://www.nist.gov/traceability/supplementary-materials-related-nist-policy-metrological-traceability.