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Metrological traceability in laboratory medicine – Report on ISO 17511-Ed2:2020

This Special Report presents the recently revised international standard ISO 17511 which has recently been published as ISO 17511-Ed2:2020, in vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples, 2nd Edition, and outlines the key changes compared to the previous 2003 version.

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JCTLM supports world-wide comparability, reliability, and equivalence of measurement results in laboratory medicine for the purpose of improving global health care by facilitating national and international trade for *in vitro* diagnostic medical devices. To accomplish this, JCTLM promotes metrological traceability of measurement results to the Système international d'unités (SI) or, where necessary, to other internationally agreed references by evaluating reference materials, reference measurement procedures and reference laboratory measurement services for conformity to appropriate international standards.

Metrological traceability in the field of laboratory medicine is defined and described in an international standard, ISO 17511, originally published in 2003 and recently revised and published as *ISO 17511-Ed2:2020*, in vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples, 2nd Edition. At the time of publication of the first version of ISO 17511 in 2003 the concept of metrological traceability in laboratory medicine was still relatively new among many medical laboratory practitioners as well as manufacturers of in vitro diagnostic devices. As such, one main focus of the initial version of this international standard was on the requirements for a manufacturer of an in vitro diagnostic medical device to describe the calibration hierarchy for their particular device (claiming to measure a stated measurand). The calibration hierarchy is based on the availability of higher order references for the intended measurand. The new version of ISO 17511 incorporates experience gained subsequent to the implementation of ISO 17511:2003, and includes updates to the standard to ensure its alignment with other relevant standards.

The main changes compared to the previous version are:

- Incorporation of requirements for the description of calibration hierarchies for measurement of catalytic concentration of enzymes (previously covered in ISO 18153:2003, now rendered obsolete).
- Clarification of the requirement that values reported on human samples shall be metrologically traceable to available higher order references, or alternative defined references in cases where higher order references are unavailable.
- Further elaboration of specific requirements for establishing and documenting metrological traceability of values assigned to calibrators and control materials, including requirements for documentation of measurement uncertainty of assigned values.
- Incorporation of a model calibration hierarchy for establishment of metrological traceability of a measurand to an international harmonization protocol, with detailed requirements now described in a new international standard, ISO 21151:2020.

The objective of establishing metrological traceability in laboratory medicine is to drive for greater equivalence among different measuring devices for the same measurand, to improve the portability of results for laboratory measurements performed in patient care,

clinical research and public health. This edition of the International standard underscores the focus on final measurement results obtained in patient care. This is reflected in the revised title, "In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples," and emphasized throughout the document. For example, the revised standard introduces the concept of 'maximum fit for purpose allowable measurement uncertainty,' (U_{max}(y)) needed in patient samples, and requires that the estimated combined expanded measurement uncertainty of final measured values not exceed U_{max}(y). This requirement aims to ensure that measurement results in patient samples are not only traceable to an available higher order reference system but also have an uncertainty of the reported values that is meaningful and relevant in patient care.

As with the previous version of the standard, whenever possible, measurement results should be traceable to the SI. For situations where this cannot be achieved, alternate calibration hierarchies are provided. Those alternatives are in general the same as defined in the previous standard. However, the revised version includes a new calibration hierarchy for cases with metrological traceability supported by an international harmonisation protocol, and refers for additional details to a new ISO standard, ISO 21151:2020 In vitro diagnostic medical devices — Requirements for international harmonisation protocols establishing metrological traceability of values assigned to calibrators and human samples. The concepts for this new calibration hierarchy were initially developed by the clinical laboratory and metrological communities (1) and the implementation of these concepts was facilitated through protocols developed by the International Consortium for Harmonization of Clinical Laboratory Results (2). Harmonization protocols were successfully applied for harmonizing measurands such as thyroid stimulating hormones (3,4). The ISO standards 17511:2020 and 21151:2020 include experiences gained from these activities.

Once an appropriate calibration hierarchy is defined and described for a given measurand, the revised standard also requires a study to validate the appropriate implementation of metrological traceability. This study needs to demonstrate that final measurement results obtained for patient samples as a result of implementing a defined calibration hierarchy are in fact metrologically traceable, with an appropriate measurement uncertainty as outlined in the standard. The standard also provides guidance on choices among different validation strategies, depending on the availability of higher order references. These validation strategies include for example the use of commutable reference materials or method comparison studies with sets of human samples using reference measurement procedures and end-user routine measurement procedures.

The new standard emphasizes that measurement procedures and materials used to establish metrological traceability should be 'fit for purpose.' The term 'fit-for-purpose' typically implies that a measurement procedure or reference material applied within a calibration hierarchy demonstrates a measurement uncertainty and a minimal bias that is consistent with the maximum allowable measurement uncertainty (Umax(y)). This means that the combined measurement uncertainty calculated using the measurement uncertainties of each component used in the calibration hierarchy does not exceed Umax(y). This requires that the uncertainties within a calibration hierarchy are well defined, which is now further emphasized in ISO standard 17511:2020.

Calibration hierarchies with well-defined measurement uncertainties can only be achieved by use of reference materials with well-characterized commutability. This point is emphasized in the standard for example in stated requirements for use of commutable reference materials where available (preferably ones that conform to requirements of ISO 15194 and listed in the JCTLM database), and with additional guidance for situations where commutable reference materials are not available. Guidance for assessing commutability of materials was published by the IFCC working group on Commutability in Metrological Traceability (5,6,7,8).

The standard also requires that reference measurement procedures and reference measurement laboratories conform with relevant ISO standards and points to the JCTLM database for lists of conforming reference measurement procedures and available reference measurement laboratories that meet requirements as specified in ISO 15193 (reference measurement procedures) and ISO 15195 (reference laboratories) respectively.

The revised standard provides additional guidance and elaboration of requirements for documenting the calibration hierarchy used for a given end-user measurement device and for the validation of the claimed metrological traceability. These requirements are aimed to achieve consistency in documentation among the many different available IVD medical devices in the market, to facilitate demonstration of metrological traceability and to support estimation of

the combined measurement uncertainty of end-user measurements where needed and/or required.

While the basic principles and approaches for establishing and documenting metrological traceability of an IVD medical device remain unchanged in the new version of ISO 17511, the revised standard was significantly revised, with some of the key changes and new requirements highlighted in this report. Despite the availability of the original version of ISO 17511 for more than 18 years, concerns remained about some end-user measurement procedures claiming metrological traceability to higher order references while demonstrating highly discordant measurement results with patient samples. To address this concern, the revised ISO 17511 was developed with more emphasis on achieving final measurement results that have a meaningful level of trueness and uncertainty appropriate to the types of clinical decisions that should be supported by a fit-for-purpose estimate of the measurand. The revised standard also provides further details and additional requirements to help ensure sustainability in the implementation of metrological traceability.

In the revised ISO standard 17511:2020, requirements for use of appropriate reference systems and higher order references in establishing metrological traceability re-emphasize the importance of the work conducted by JCTLM, with the inclusion of multiple references to the JCTLM databases in the revised standard. The revised standard provides necessary updates, includes needed requirements, and strongly emphasizes the importance of choosing measurement procedures that are fit-for-purpose. Since intended medical use of a given measurand may change over time as new treatments, clinical guidelines and research findings become available, the implementation and sustainment of a metrologically traceable calibration hierarchy in a meaningful manner as outlined in the revised ISO 17511 standard should always be undertaken in close collaboration with the relevant medical experts.

DISCLAIMER

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry. Use of trade names is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention, the Public Health Service, and the US Department of Health and Human Services.

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