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Documenting metrological traceability as intended by ISO 15189:2012: A consensus statement about the practice of the implementation and auditing of this norm element

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Abstract: ISO15189:2012 requires medical laboratories to document metrological traceability of their results. While the ISO17511:2003 standard on metrological traceability in laboratory medicine requires the use of the highest available level in the traceability chain, it recognizes that for many measurands there is no reference above the manufacturer's selected measurement procedure and the manufacturer's working calibrator. Some immunoassays, although they intend to measure the same quantity and may even refer to the same reference material, unfortunately produce different results because of differences in analytical selectivity as manufacturers select different epitopes and antibodies for the same analyte. In other cases, the cause is the use of reference materials, which are not commutable. The uncertainty associated with the result is another important aspect in metrological traceability implementation. As the measurement uncertainty on the clinical samples is influenced by the uncertainty of all steps higher in the traceability chain, laboratories should be provided with

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adequate and appropriate information on the uncertainty of the value assignment to the commercial calibrators that they use. Although the between-lot variation in value assignment will manifest itself as part of the long-term imprecision as estimated by the end-user, information on worst-case to be expected lot-lot variation has to be communicated to the end-user by the IVD provider. When laboratories use ancillary equipment that potentially could have a critical contribution to the reported results, such equipment needs verification of its proper calibration and criticality to the result uncertainty could be assessed by an approach based on risk analysis, which is a key element of ISO15189:2012 anyway. This paper discusses how the requirement for metrological traceability as stated in ISO15189 should be met by the medical laboratory and how this should be assessed by accreditation bodies.

Keywords: metrological traceability; risk management.

Background

Results provided by medical laboratories have an important role in medical decisions [1]. Because results are compared to reference intervals, decision limits or with earlier results that may have been established elsewhere in the care process, it is important that results are equivalent (within stated specifications). Metrological traceability to a certified reference material and/or reference procedure should assure equivalence of patient results across time, space and measuring systems [2–8].

The ISO/IEC guide on International Vocabulary of Basic and General Terms in Metrology (VIM- 2012) [9] defines metrological traceability as: "*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*".

ISO 15189:2012, which specifies requirements for quality and competence in medical laboratories, requires laboratories to verify and document the metrological traceability of calibration of their measurement procedures [10]. Hence, accreditation to this standard by the national accreditation bodies requires verification whether this is done properly. The International Laboratory Accreditation Cooperation (ILAC) has issued a policy on the assessment of metrological traceability of laboratory results [11]. As national accreditation bodies that have signed the multilateral agreement between international accreditation bodies have to comply with ILAC policies, the requirements of these policies are relevant to all parties involved as they are essential for harmonization of ISO15189 accreditation [12].

Ideally, measurement procedures are traceable to the International System of Units (SI), but for many measurands in medical laboratories, this is not achievable. To cope with these specific challenges, specific ISO standards have been developed, i.e. ISO17511:2003 "In vitro diagnostic medical devices – Measurement of quantities in biological samples – Metrological traceability of values assigned to calibrators and control materials" [13] and ISO 18153:2003 "In vitro diagnostic medical devices – Measurement of quantities in biological samples – Metrological traceability of values for catalytic concentration of enzymes assigned calibrators and control materials" [14]. The ISO 17511 standard states that "*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*" [13]. Furthermore, ISO 17511 cautions that "*… it is important to recognize that different procedures purporting to measure the same quantity may in fact give different results when applied to a particular sample or reference material. This may arise, for example, when two or more immunoprocedures purporting to measure the concentration of a hormone such as thyrotropin (thyroid stimulating hormone, TSH) are applied to a reference material of the hormone, because the respective reagents recognize and react to different extents with various epitopes in the material, thus leading to results for different although related quantities*" [13].

The immunoassay example mentioned illustrates that many variables can contribute to differences among laboratories' results. These may arise, e.g. from the following:

1. The manufacturer's product calibrator, which is traceable to a given higher order reference material (or higher order reference measurement procedure);
2. The laboratory routine measurement procedure (method);
3. The source of reagents (same manufacturer or third party);
4. The analytical instrumentation used.

The current ILAC policy on the assessment of metrological traceability, although released in 2013, lacks any reference to ISO 17511 or to relevant challenges encountered in the documentation of metrological traceability for typical measurands in laboratory medicine [11]. Therefore, its use as a guideline for the assessment of metrological traceability in medical laboratories may give rise to discussions

or even disputes between laboratories and assessors when no other documented instructions are provided to the assessors that cope with these specific challenges.

To deal with the specific issues concerning measurands of importance in laboratory medicine, the American Association for Laboratory Accreditation (A2LA) has published in 2014 a policy on metrological traceability especially for medical laboratories, seeking ISO 15189 accreditation [15], as an additional document to their "Policy on Metrological Traceability" [16].

ISO 15189:2012 requirements about metrological traceability

With the challenges mentioned in ISO 17511 and the specific requirements of the A2LA for the assessment of medical laboratories in mind, we will comment on the intent of paragraph 5.3.1.4 of ISO 15189:2012 concerning "Equipment calibration and metrological traceability" [10] in a point by point approach.

"*The laboratory shall have a documented procedure for the calibration of equipment that directly or indirectly affects examination results. This procedure includes: a) taking into account conditions of use and the manufacturer's instructions… "*. This is not the first point by accident. In medical laboratories, measurements for most tests are performed with CE-marked *in vitro* diagnostics medical devices (IVD-MD) (or FDA approved in USA) according to manufacturer's instructions. The new IVD-MD regulation recently released by the European Union Parliament states that manufacturers are responsible for establishing and documenting traceability of the commercially available assays [17]. Those requirements are now more explicitly formulated, as the requirements in the previous version gave too much room for (unintended) noncompliance [18]. If clinical laboratories are compliant with the manufacturer's instructions, they only have to verify whether the manufacturer properly established and specified the traceability data for the used calibrators [19]. Documented procedures should be available on how to comply with the manufacturer's instructions. Procedures on how to verify whether the manufacturer's calibration is according to the claimed metrological traceability and how to verify that this calibration is stable over time are covered by ISO 15189 items 5.5.1.2 and 5.6.2 on verification of measurement procedures and quality control, respectively. Assessment of such procedures should be performed with regards to those elements of the standard.

"b) Recording the metrological traceability of the calibration standard and the traceable calibration of the item of equipment". The emphasis in this item is on the word "recording". It does not require "determination". What is asked is that laboratories record the traceability by documenting which higher-order reference in the traceability chain is used.

"c) Verifying the required measurement accuracy and the functioning of the measuring system at defined intervals". The "required measurement accuracy" is a term from ISO 15189:2012 paragraph 5.5.1 requiring laboratories to select, verify or validate examination procedures that meet the criteria selected for the intended use of the test. This includes criteria for measurement trueness and precision, which together define accuracy. When the measuring system fulfil these predefined criteria, it may be used in clinical settings. To ensure that the criteria are also met in the future, the ISO standard requires verification at defined time intervals. This may be achieved by using data from quality control as required by paragraph 5.6.2. If quality control results show that accuracy or one of its components has worsened since validation of examination procedure, but still meets the predefined acceptance criteria, the measuring system may be used. If the criteria are no longer met, the laboratory have to find the cause, implement the corrective action or discontinue the method for clinical use if no improvement is recorded. This also relates to measurement uncertainty in paragraph 5.5.1.4., which is closely linked to traceability. Paragraph 5.5.1.4 does not intend calculation and documentation of measurement uncertainty to be a one-time exercise, but to provide data that enables the laboratory staff to judge continuously whether a measuring system meets the acceptance criteria [20].

"d) Recording the calibration status and date of recalibration". Like the element b), this point concerns the recording of information. Calibration is an event that can significantly affect results. The purpose of recording all calibrations is to be able to reconstruct and audit whether the laboratory adequately manages these events. This facilitates troubleshooting by the laboratory whenever individual or multiple results give rise to doubts about their plausibility, for instance because of unexpected differences between earlier or later results.

"e) Ensuring that, where calibration gives rise to a set of correction factors, the previous calibration factors are correctly updated". Laboratory medicine specialists may consider this point trivial, but laboratory staff should always be aware of the calibration mechanism used. Before a new calibration, laboratorians should make sure that the parameters of the equation include the factors of the previous

calibration, as the applied calibration curve must reflect all the applicable factors to trace the result up to the original calibration.

"f) Safeguards to prevent adjustments or tampering that might invalidate examination results". This point is repeated in several places in the ISO standard as part of management responsibilities for regulating responsibilities and authorization of staff and access control in instrument (analytical platform) software-systems or laboratory information systems.

"Metrological traceability shall be to a reference material or reference procedure of the higher metrological order available". The most important word here is "available". Other than in physical testing or analytical chemistry, in medical laboratory testing the higher metrological order available may be the method itself. ISO 17511 states: *"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"*.

"NOTE Documentation of calibration traceability to a higher order reference material or reference procedure may be provided by an examination system manufacturer. Such documentation is acceptable as long as the manufacturer's examination system and calibration procedures are used without modificatio.". This note is very clear about the intentions of the standard. Apart from requirements mentioned in element 5.5.1.2 on method verification, there is no need to confirm by experiment the information that is provided by the manufacturer as long as the measurement system is used according to the manufacturer's instruction. This is in line with the A2LA policy for metrological traceability in ISO15189, but unfortunately it is totally neglected by the ILAC policy P10:2013.

"Where this is not possible or relevant, other means for providing confidence in the results shall be applied, including but not limited to the following:

- *use of certified reference materials;*
- *examination or calibration by another procedure;*
- *mutual consent standards or methods which are clearly established, specified, characterized and mutually agreed upon by all parties concerned"*. These sentences make clear what should be managed, i.e. the "confidence in the results". By stating that other means can be used, and not limiting the other means to the provided list, the authors of the standard emphasize that the main requirement of the paragraph is to establish confidence in the relationship between results and their intended metrological traceability.

A role for risk management

The focus on "providing confidence in the results" in the last clause is also visible in the first clause where the documentation of metrological traceability is limited to those calibrations and equipment "that directly or indirectly affect the examination result". As indicated in NOTE 1 of paragraph 5.3 of ISO 15189:2012, *"the laboratory equipment includes hardware and software of instruments, measuring systems, and laboratory information systems"*. Ancillary equipment, such as pipettes, thermometers, CO_2 pressure sensors, etc. should be considered as hardware and therefore as part of the laboratory equipment. Whether this means that all (or at least some) ancillary equipment should have documented metrological traceability is often subject of dispute between medical laboratories and assessors. The A2LA offers a practical solution by stating that *"if a piece of ancillary equipment is not critical to the result, such as using a pipette to aliquot a sample for storage, that ancillary equipment is exempt from this policy"* [15].

To determine whether a piece of equipment is critical, ISO 15189:2012 has its own solution in the form of risk management as indicated in the 4.14.6 paragraph. Therefore, the question whether equipment does affect or not results should be evaluated on the basis of the severity and ease of error detection. A good system of risk management will differentiate between ancillary equipment that needs documented metrological traceability or not. Depending on the circumstances of use an identical piece of equipment may or may not be prone to such documentation. More in general, risk management can be applied all over the standard to resolve questions on choices made in required procedures. This ranges from the frequency of internal audits to the retention time of documents. The standard requires laboratory management to establish policies that meet the appropriate need. The only tool to establish the appropriate need is risk management.

When we apply risk management to metrological traceability in a medical laboratory we start with the intention of underpinning the requirement for documentation of metrological traceability, namely transferability over time and space. That requires: (1) documentation of the traceability to the highest possible reference level for a given measurand and (2) periodic verification that the documented traceability is still in place.

The documentation of traceability should not give rise to much ambiguity. The most obvious place to document metrological traceability is as a part of the process of method verification or method validation. In paragraph 5.5.1.3 on validation, trueness is listed as a typical performance characteristic. As definition of trueness requires an anchor to which trueness should be verified, it is obvious that only documentation of the metrological traceability would provide such an anchor. Medical laboratories should document to which higher order references the measuring system that they use is traceable and the IVD provider will or should provide such information. For example, the calibration of a creatinine assay can be traceable to the isotope dilution mass spectrometry reference method. This implies that IVD manufacturers should provide such information in the package insert or at least make available upon request. In cases where the highest level of the traceability chain is the calibration provided by the IVD manufacturer, this should be clearly documented. Laboratory directors should have in mind the existence of different quality among assays for each test due to difference in calibrator measurement uncertainty value and select only those products with acceptable measurement uncertainty [21]. Assessors have no authority for changing the laboratory policy about the chosen measurement procedure. They are allowed only to check if laboratory staff reviewed all critical data, has selected a method that is suitable for the intended use in terms of its performance characteristics, and informed customers in a proper way about all relevant data which might have influenced the test results.

Whether the IVD product has a bias compared, e.g. to the reference measurement procedure and whether this bias is small enough to make the test suitable for the intended use is the concern of method verification as documented in paragraphs 5.5.1.2 and 5.5.1.3, which also check whether the uncertainty including the medically not relevant bias is acceptable. Tolerance limits for allowable bias and imprecision are judged by the specialist in laboratory medicine in the light of the intended use, supported by guidelines of the scientific societies on laboratory medicine [22, 23]. Quality control procedures as documented in paragraph 5.6.2 should use these performance specifications and check that performance is for the intended use as during verification/validation. The acceptable bias and imprecision define acceptable inaccuracy in a single measurement and can be expressed as measurement uncertainty [20, 21]. Laboratories have procedures for internal quality control (5.6.2) and external quality assessment (5.6.3) to make sure that their measurement uncertainty does not exceed the acceptance criteria of the validation/verification [24, 25].

Measurement uncertainty

The concepts of measurement uncertainty and metrological traceability are interrelated. Although the debate on how to calculate and express measurement uncertainty is – like the fundamentals of metrological traceability – outside of the scope of this paper, and depends on harmonization by itself [20, 24, 26] we do have to discuss its impact on ISO 15189 accreditation assessment. In ISO 17511:2003, it is clearly stated and graphically depicted that each single step of the traceability chain comes with its own uncertainty [6, 7]. For the results by the end-user procedure at the bottom of the chain, the total measurement uncertainty comprises accumulation of all the uncertainties of the chain. This means that the measurement uncertainty of the end user procedure is a combined figure that, at least partially, cannot be influenced by the end user itself. Braga and Panteghini [24] turn around that concept by introducing a budget model where the intended use defines acceptable analytical performance criteria for measurement uncertainty [21]. This budget of uncertainty should be distributed between the individual steps of the traceability chain involved. In such an approach the uncertainty of end user procedure is not a result that has to be accepted, but a predefined goal that should be achieved in dialogue with the higher steps of the chain [20]. Braga et al. has proposed that no more than one third of the total uncertainty budget, established by appropriate analytical performance specifications, is consumed by the uncertainty of reference materials and no more than 50% of the total budget is consumed by the manufacturer's calibration and all higher steps in the chain [21, 24]. The remaining part of the total uncertainty budget should be available for the measuring system imprecision (including the lot to lot variation of the reagents) and individual laboratory performance to fulfill the uncertainty goal. The new European IVD regulation requires manufacturers to document the complete metrological traceability chain as well as the between-lot variation in terms of measurement uncertainty [21]. Professional IVD users represented by their scientific associations, the IVD industry and the national standardization bodies collaborate in the appropriate ISO technical committee (ISO TC212) to formulate definitions on how to express the uncertainty of the individual steps of the traceability chain and how to distribute the budget as defined by the intended use of the individual tests.

Conclusions

The main scope of this paper is to encourage ILAC to revise its recommended policy for the assessment of metrological traceability in medical laboratories seeking ISO 15189 accreditation. The P10:01/2013 document claims applicability to medical laboratories with ISO 15189 accreditation, but lacks reference to ISO 17511 standard, which mentions relevant challenges when documenting metrological traceability in medical laboratories. In particular, the accreditation policy should allow for risk mitigation by other means that are already obligatory in the accreditation process such as internal quality control, external quality assessment and risk management. Meanwhile laboratories and assessors are encouraged to think and act in anticipation of the suggested improvements.

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