

Uncertainty From Sampling: Could the Requirements of ISO/IEC 17025 (2017) Be Adopted in Medical Laboratories?

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ABSTRACT

ISO/IEC 17025:2017 and ISO 15189:2012 specify the requirements for the competence of laboratories. The former refers to laboratories in general, whose activities include testing, calibration, and sampling followed by testing or calibration while the latter refers to medical laboratories. Despite the differences between the two standards reflecting the specific needs each of them is addressing, the development of these two documents has, until now, followed similar paths. In this presentation, the requirements of ISO/IEC 17025 referring to sampling and the uncertainty arising from it are presented underlining what testing laboratories need to consider. In addition, a comparison with the requirements of ISO 15189 with regard to sampling and measurement uncertainty is made. Based on this, the question whether an approach on uncertainty from sampling similar to the one introduced by the new ISO/IEC 17025 can be included in the revision of ISO 15189, currently under way, is addressed.

KEYWORDS

Accreditation, Measurement Uncertainty, Testing Laboratories, Uncertainty From Sampling

INTRODUCTION

The new ISO/IEC 17025 (2017) has introduced several changes to the 2005 version of the standard in the text itself and the philosophy (Eurachem, 2018). Some of the additional provisions are pretty new, e.g., sampling in the accreditable activities, risk-based thinking, the use of a decision rule, and some management aspects. However, there are also many changes to other requirements already existing, e.g. traceability issues, ensuring the validity of results (Eurachem leaflet, 2018).

While the transition period for implementing the new standard is over, laboratories tried to find their way to address all the new requirements adequately. At the same time, accreditation bodies needed to ensure their readiness to assess laboratories against the new standard. Last but not least, EA and other regional bodies need to ensure that peer evaluation procedures are adjusted so that they are carried out in a harmonised way.

The procedure for revising ISO 15189 (2012), i.e. the standard for medical laboratories, is in progress; the task is expected to be finalised by the end of 2022. Despite the differences between the two standards reflecting the specific needs each of them is addressing, the development of the two documents has followed similar paths until now.

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BACKGROUND

Some of the new provisions of ISO/IEC 17025 are similar to those of ISO 15189. These refer to risks and opportunities (risk-based thinking vs risk management), control of data and information management (more detailed requirements, addressing new technology tools), the competence of proficiency testing schemes of providers and reference materials producers based on their compliance with the relevant standards, i.e. ISO/IEC 17043 (2010) and ISO 17034 (2016) respectively.

Although the revision of ISO 15189 is still going on, some comments on the possible outcome can be made. It is considered that some of the new provisions of ISO/IEC 17025 will be included in the revised edition of the standard for medical laboratories, adapted as appropriate.

Uncertainty from Sampling in ISO/IEC 17025

The inclusion of sampling as a stand-alone laboratory activity, although not expressed in this way, represents one of the main changes compared with the 2005 version of ISO/IEC 17025. That is reflected in several other provisions of the new standard, mainly those referring to measurement uncertainty (Tsimillis, 2018).

Sub-clause 7.6.1 specifies that, when evaluating measurement uncertainty, all contributions of significance, including those arising from sampling, shall be considered.

Sub-clause 7.8 specifies the requirements for reporting results; sub-clause 7.8.2 includes standard requirements for all reports, namely test, calibration or sampling. Among others, it is required that the date of sampling shall be included where this is critical to the validity and application of the results (sub-clause 7.8.2.1.h); similarly, reference to the sampling plan and sampling method shall be included where these are relevant to the validity or application of the results (sub-clause 7.8.2.1.k). If the laboratory has not been responsible for the sampling stage, a statement shall be included that the results apply to the sample as received (sub-clause 7.8.2.2). Additional requirements for each type of the said laboratory activities are included in sub-clauses 7.8.3 (testing), 7.8.4 (calibration) and 7.8.5 (sampling). The latter applies if the laboratory is responsible for the sampling activity and, where necessary, for interpreting results. Points (a)-(e) refer to details of the sampling procedure that shall be included in the report, i.e. date, identification of the item or material sampled, the location of sampling, the sampling plan and method, as well as details of any environmental conditions during sampling that affect the interpretation of the results. Last but not least, according to point (f), information required evaluating measurement uncertainty for subsequent testing or calibration shall be included in the report as well.

Testing laboratories trying to meet ISO/IEC 17025 requirements may find some approaches addressing the uncertainty from sampling (Ramsey et al., 2019; Magnusson et al., 2020) helpful. These approaches are applicable when the measurand is defined in terms of the analyte concentration in the sampling target, rather than just the sample delivered to or tested by the laboratory. These approaches are based on replicate sampling, which is appropriate for analytical laboratories, but they may not readily apply in all cases in medical laboratories, as we shall see later. At the same time, trying to answer this presentation's central question, we need to elaborate on the requirements of ISO 15189 for sampling and measurement uncertainty.

What Does ISO 15189 Provide for Sampling?

In medical laboratories, the relevant standard ISO 15189 emphasises the pre-examination processes (preanalytical phase), mainly sampling, including patient-collected samples and handling of samples. These factors inevitably contribute to the measurement uncertainty; therefore, the measurement result (and its significance) might be compromised. Thus, according to the said standard, medical laboratories shall have documented procedures and information for pre-examination activities, referring to all relevant aspects. These are presented in Table 1. The implementation of these provisions is further supported by ISO/TS 20658 (2017).

Table 1. Basic requirements of ISO 15189 regarding the pre-examination processes related to sampling and sample handling

Aspect	Basic provisions
Information for patients and users of its services (sub-clause 5.4.2)	<ul style="list-style-type: none"> • the location and opening hours of the laboratory • the examinations offered by the laboratory, including, as appropriate, information concerning samples required, primary sample volumes, special precautions etc. • instructions for completion of the request form • instructions for preparation of the patient • instructions for patient-collected samples • instructions for preparation of samples, including any special needs • the laboratory's criteria for accepting and rejecting samples • a list of factors known to significantly affect the performance of the examination or the interpretation of the results
Request form information (sub-clause 5.4.3)	<ul style="list-style-type: none"> • patient identification • type of primary sample and, where relevant, the anatomical site of origin • clinically relevant information about the patient and the request, for examination performance and result interpretation details date and, where appropriate, time of primary sample collection • date and time of sample receipt
Primary sample collection and handling (sub-clause 5.4.4)	<ul style="list-style-type: none"> • the proper collection and handling of primary samples these shall be available to those responsible for primary sample collection whether or not members of the laboratory staff (sub-clause 5.4.4.1) • instructions for pre-collection activities (sub-clause 5.4.4.2) • instructions for collection activities (sub-clause 5.4.4.3)
Samples transportation (sub-clause 5.4.5)	<ul style="list-style-type: none"> • monitoring the transportation of samples within an appropriate time frame and temperature interval, the use of designated preservatives to ensure the integrity of samples and how to ensure the safety of the carrier, the general public and the receiving laboratory sample
Sample reception (sub-clause 5.4.6)	<ul style="list-style-type: none"> • criteria for acceptance or rejection of samples
Sample handling, preparation and storage (sub-clause 5.4.7)	<ul style="list-style-type: none"> • securing patient samples integrity during pre-examination activities, handling, preparation and storage • time limits for requesting additional or further examinations

How Does ISO 15189 Address Measurement Uncertainty?

Uncertainty in the pre-examination processes is attributed to preanalytical variation and, sometimes, biological variation (Theodorsson & Magnusson, 2017), referring to the variance in test results within a single individual over a specified period. It is understood how important this phase is and the extent to which several factors during this phase can result in nonconformities and failures. Despite the great emphasis given to the pre-examination processes concerning measurement uncertainty, ISO 15189 focuses only on contributions arising from the examination phase, excluding those deriving from the pre-examination processes. This is clearly stated in sub-clause 5.5.1.4 and, particularly, in Note 1 indicating that: “The relevant uncertainty components are those associated with the actual measurement process, commencing with the presentation of the sample to the measurement procedure and ending with the output of the measured value”.

What Is Expected from the Revision of ISO 15189?

It is expected that some of the new elements of ISO/IEC 17025 are to be taken into account during the revision of ISO 15189, e.g. management issues, metrological traceability, widening the risk-based thinking, additional tools to ensure the validity of results, the meaning of “shall”, “should”, “may”, “can”. Could we expect that sampling will be considered as a stand-alone activity in the medical sector? A similar definition to the one given in ISO/IEC 17025 for laboratories, including sampling

among their activities, could indeed apply in medical laboratories as well. This may also serve cases of point-of-care testing (ISO 22870, 2016)

What about uncertainty from sampling? Could the requirement consider the contribution arising from sampling when evaluating measurement uncertainty applied to medical laboratories? It seems that approaches applicable in testing laboratories referred to above (Ramsey, Ellison, & Rostron, 2019; Nordtest, 2007) could not apply in all medical laboratories and the whole range of activities. That is due to some inherent difficulties arising from the particular type of sample and the procedure for its collection.

DISCUSSION

In medical laboratories, the pre-examination processes are considered the most important ones. According to ISO 15189, they start from the clinician's request and include the examination request and identification of the patient, primary sample collection and transportation to and within the laboratory and end when the analytical examination begins. They are related to factors not always under the control of the laboratory, even unknown in some cases, resulting in the highest percentage of failure of the results. The integrity of the sample is related to the interval and the conditions during its transfer to the laboratory. Before this, the proper preparation of the patient is another crucial factor. The laboratory should prepare and use the primary sample collection manual. This manual contains all necessary information and instructions regarding all examinations offered, e.g. patient preparation, primary sample collection, identification, transfer and storage of primary samples etc. The whole trip from the collection location to the laboratory needs to be monitored about the appropriate conditions for each case. Upon reception at the laboratory, all samples need to be registered, accompanied by details of who collected/ received them. The laboratory should ensure that samples are stored under appropriate conditions so that repetitive or additional examination could be carried out if needed. If the patient receives any medication, the laboratory is recorded and taken into consideration when the results are discussed (Tsimillis & Michael, 2014).

Preanalytical errors account for up to 70% of all mistakes made in laboratory diagnostics (Plebani, 2012). These errors are primarily due to non-compliance with the relevant procedures and instructions; however, not all of them produce measurement uncertainty. Some of them make the examination impossible, e.g. insufficient volume of the sample or haemolysed samples; to this end, appropriate quality indicators (Plebani, 2012) are the primary tool to avoid/minimise such problems according to sub-clause 4.14.7 of ISO 15189 where it is specified that "The laboratory shall establish quality indicators to monitor and evaluate performance throughout critical aspects of pre-examination, examination and post-examination processes". The example given in the said sub-clause refers to the number of unacceptable samples, number of errors at registration and/or accession, number of corrected reports. These can be further analysed concerning the details in each case (Plebani et al., 2015).

Sampling is often an activity carried out in the medical laboratory; this is especially the case in small private laboratories. This is not the case in hospital laboratories where the sample collection is out of the control of the medical laboratory. However, in cases where the medical laboratory staff does not collect samples, laboratories are still responsible for ensuring that samples are not compromised (ILAC, 2018).

Many different types of samples extensively differentiate the collection procedure (Lab Tests Online, 2019) and the sampling technique. Repetitive samples cannot be ensured for reasons explained below. In some cases, samples are easy to collect and do not cause discomfort to the patient; they are mainly those naturally eliminated from the body, i.e. semen, sputum, stool, urine, saliva, vomitus, oral fluid or sweat. Some others are collected with some discomfort for the patient, i.e. those collected by simply a swab, i.e. secretions and tissues from the female reproductive system tract, secretions and fluids from the nose or throat, samples from open wounds and sores/ulcers. Other samples can only be obtained by some invasive technique and inevitably with varying discomfort for the patient,

i.e. blood, tissue biopsy, cerebrospinal fluid, other body fluids, bone marrow, amniotic fluid. In such a case, the patient suffers pain, discomfort and/or anxiety. Such techniques, e.g. lumbar puncture, thoracocentesis, amniocentesis, peritoneocentesis (or laparocentesis), require specific expertise. All these cases fall within the scope of a medical laboratory which, according to the definition given in ISO 15189, examines “materials derived from the human body”.

Several publications deal with the uncertainty from sampling (Theodorsson & Magnusson, 2017; Ramsey & Ellison, 2017; Kallner, 2001), but only a few address this issue in a practical way to quantify the uncertainty arising from it. The easy access to samples does not necessarily mean that sampling replication is realistic, bearing in mind ethical issues. The following examples are characteristic:

When the sample to be collected is urine, multiple samples can be collected quickly, following an appropriate schedule. That can provide the basis for statistical analysis and evaluation of the uncertainty component arising from sampling (Fuentes-Arderiu, 2002).

In blood sampling, biological variation may reflect the variation caused by different body positions and difference in the point from where the blood sample is collected. This is an exciting component that needs to be taken into account; this can be achieved by multiple sampling, despite the inconvenience for the patient (Narayanan & Guder, 2001).

Concerning pathology examination, multiple samples are needed due to their heterogeneity (Kim & Tsao, 2014). That introduces the need for specific training, experience and expertise and a complicated technique. Detailed protocols describing the sampling procedure must be followed. Relevant examples refer to prostate, liver, lungs, etc., where invasive sample collection techniques are used; it is not easy/realistic for the procedure to be repeated in such cases. Even if several samples are obtained, biopsies may still miss malignant cells, leading to false-negative results (American Cancer Society, 2019).

Two issues illustrate additional difficulties impacting the uncertainty arising from sampling, which cannot be included in the overall evaluation of measurement uncertainty. Sub-clause 5.4.4.2 f) of ISO 15189 specifies that, when needed, the sample collection time is recorded. However, according to a survey carried out by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) in 2017, this is not homogeneously addressed by laboratories in Europe (von Meyer et al., 2020). On the other hand, it was realised that standardised protocols for patient preparation (fasting) for laboratory examination were lacking (Simundic et al., 2014). Significant heterogeneity exists in the definitions of “fasting”, which impacts uncertainty for evaluating which is not considered.

During the SARS-CoV-2 pandemic, millions of tests have been carried out all over the world. The most widely used method of sample collection refers to swabbing the back of the nose. However, an essential factor not directly related to the sample collection is the time from the suspected, if any, infection to sampling. Recently, self-testing is also an alternative, using a nasal or a saliva specimen. In all cases, questions may arise from the possible flaws.

It has been reported that in a study for the prediction of total serum bilirubin levels in newborn infants, measurement of transcutaneous bilirubin (TcB) was obtained on the infants' forehead using a transcutaneous jaundice detector (Ercan & Özgün, 2018). Multiple readings were performed at different points of the forehead, and the average of values was recorded. However, although this measurement comes under the medical sector, it does not represent a medical laboratory examination within the meaning of ISO 15189, bearing also in mind that, in this case, there is no primary sample which is defined as “a discrete portion of a body fluid, breath, hair or tissue taken for examination, study or analysis...” as defined in ISO 15189.

Despite the difficulties, uncertainty from sampling cannot be ignored, but it is feasible to be taken into account quantitatively only in some cases in medical laboratories.

CONCLUSION

Uncertainty arising from sampling is a significant component in measurement uncertainty for all testing laboratories. ISO/IEC 17025 introduces the requirement to take into account this component when evaluating measurement uncertainty. Testing laboratories, based on publications available (Ramsey et al., 2019; Magnusson et al., 2020), were expected to adequately address this requirement and all other requirements of ISO/IEC 17025 within the set transition period. Uncertainty arising from sampling is of interest to medical laboratories as well, bearing in mind that the diagnosis needs to be reliable not only concerning the sample(s) examined but mainly for the patient himself/herself. Concerning medical laboratories, ISO 15189, which is currently under revision, does not provide uncertainty in the pre-examination processes. Despite inherent difficulties, varying with the type of sample, there are cases where uncertainty from sampling can indeed be considered when evaluating measurement uncertainty and laboratories are encouraged to proceed towards this task. However, there are cases where this task is not feasible. In all cases, medical laboratories shall ensure that the appropriate procedures addressing all issues regarding sampling and samples are fully implemented by adequately trained personnel. Based on the above discussion, it is not expected that an approach on uncertainty from sampling similar to the one introduced by the new ISO/IEC 17025 could be adopted in the current revision of ISO 15189.

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