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GUIDELINES FOR THE MEASUREMENT UNCERTAINTY IN MEDICAL TESTING

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Purpose

This document describes the requirements and regulation of health and safety, which may be applied at Laboratories Performing Calibration and Measurements, to assure the safety of employees, and protect them against chemical and hazardous materials.

Scope

Health and safety requirements are applied to personnel working at laboratories performing with calibration and testing activities.

Authorship

This publication has been written by the Technical Committee, and approved by the Accreditation Director.

Official language

The text may be translated into other languages as required. The English language version remains the definitive version.

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Further information

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1. Introduction

When the medical laboratory produces a test result, the reported value is NOT considered the TRUE concentration of the measurand. Rather, it is the medical laboratory's best estimate of the true value that, with a certain level of confidence, lies somewhere within an interval of values characterized by measurement uncertainty. This forms the grounds on which ISO 15189 thought it was necessary for medical laboratories to calculate and report this statistic (measurement uncertainty). Being able to provide the physician, on request or as needed, the measurement uncertainty associated with a particular test value helps the physician determine whether the patient is sick or well, the prognosis is good or bad, the treatment is effective or not effective. The measurement uncertainty is particularly helpful in differentiating whether a change in a serial test result is due to analytical variation or a true physiological change.

Measurement uncertainty provides a framework for objectively estimating the reliability of results produced by any given measurement system. When measurements are repeated, some variation of the results will be observed due to random variation of the measurement conditions. The differences will be noticeable if the sensitivity and resolution of the measuring system is sufficient. Therefore, for measurement results to be useful, such result variability (uncertainty) needs to be quantified so that those performing measurements and those receiving results have an objective estimate of the quality (reliability) of the results produced.

Within the laboratory, knowledge of the sources of uncertainty and their relative magnitude may also provide opportunities for modifying a measurement system to improve the quality of results.

Although in practical work, clinical experience may suffice, medical laboratories may wish to make measurement uncertainties available to clinical users for improved patient management.

In summary, measurement uncertainty helps clinicians in clinical diagnosis such as comparison of a result to reference intervals or decision limits, in patient monitoring with same or different uncertainties. At the same time, it helps laboratories identify sources of variation in results and or

technical steps in which uncertainty potentially can be reduced.

Although pre and post-analytical variables as well as biological variation have impact on the test results, these variables are not included in the estimation of measurement uncertainty. However, laboratories must have standardized procedures for minimizing pre and post-analytical variables. It is a crucial that these variables are assured before proceeding with technical evaluation of measurement uncertainty provided by a given laboratory. Moreover, a successful internal quality control and external quality assurance act as a qualifier for an appropriate estimation of measurement of uncertainty, and failure in any represents inconsistent system and may nullify measurement uncertainty estimation unless timely and proper justification and corrective actions are satisfactory.

2. Potential sources of measurement uncertainty

The following sources that may contribute to measurement uncertainty are limited to the measuring phase and do not address pre and post-analytic factors or biological variation.

Sources of measurement uncertainty may associated with purchased reagents are such as assigned value of calibrators, lot-to-lot variations in reagent response, stability of reagents and calibrators, commutability of calibrators and reference materials. Sources of measurement uncertainty associated with measurement procedures may include frequency of calibration and maintenance. Sources of measurement uncertainty associated with laboratory personnel may include deficiencies in education and training, lack of compliance with procedures/instructions or lack of manual dexterity, eg, pipetting

3. Approaches to the estimation of measurement uncertainty

Measurement uncertainty can be estimated by the bottom-up or top-down approaches. The bottom-up approach suggests that all possible sources of uncertainty are identified and quantified. A combined uncertainty is calculated using statistical propagation rules. The bottom-up procedure may be more useful during method development. The size of each of the uncertainty contributions may be estimated by statistical analysis of measured quantity values (Type A) or

by other methods, eg, literature, and equipment and product specifications (Type B). This approach is often referred to as the GUM approach. The top-down approach directly estimates the measurement uncertainty results produced by a measuring system as one piece, typically, by evaluation of experimental data such as QC data, or data from a method verification experiment. The top-down approach estimates the entire process by a Type A or a Type B estimation. The top-down approach is robust against incomplete models and/or underestimated components in the model. It is also suitable for developed methods or verification experiments. This approach is particularly well suited to the closed measuring systems commonly encountered in routine medical laboratories.

- Type A: an estimate based on statistical analysis of a series of measurements,. The u(x) is equal to the SD of such results.
- Type B: an evaluation of uncertainty by means other than statistical analysis, eg, from one's own previous studies on related measuring systems, manufacturers' data, the literature, or professional judgment

Ideally, the uncertainty estimated by the top-down and bottom-up approaches should be interchangeable. If top-down estimates suggest that performance targets have not been met, the bottom-up approach can be used to identify potentially modifiable sources of uncertainty. The outcome should ideally be the same. But the bottom-up system allows a systematic approach to improvement of the performance. Whichever route is chosen, the laboratory should always verify the model. If the bottom-up model is chosen, it should always be verified by the top-down procedure; if the top-down route is chosen and the results are found to be acceptable, nothing more needs to be done. However, if this approach is unsatisfactory, a systematic search for the root cause should be performed by the bottom-up procedure.

4. Estimation of Measurement uncertainty:

Estimation of the measurement uncertainty starts with estimation of the standard uncertainty often calculated from quality control data such as standard deviation/literature or combination of both. When more than one contributor leads to the generation of the final result, standard uncertainties associated with all contributors are then combined/propagated to calculate the combined uncertainty; propagation may be obtained using standard propagation of error rules (the square

root of the sums of squares of SDs known as the “root sum of squares” - RSS. Combined uncertainty is then multiplied by coverage factor to increase the level of confidence; a coverage factor of 2 increases the confidence level 95% and generating what is called expanded uncertainty.

An uncertainty profile covering the measuring range of the assay is recommended where each result is reported with its corresponding measurement uncertainty. Alternatively, the measurement uncertainty estimated from the closest quality control level should be reported along with the patient result.

Whenever a qualitative test result is reported based on measured quantitative value in relation to a given cutoff, the measurement uncertainty associated with the quantitative value should be calculated and made available to clinicians upon request.

While ISO 15189 does not request providing measurement uncertainty for qualitative tests results directly generated based on direct observation of the result such as a change in color or agglutination/lattice formation, sensitivity and specificity of the assay provided by the manufacturer may provide some data on measurement uncertainty in case requested by the clinician.

For medical laboratory examinations, imprecision estimates such as standard deviation (SD) and coefficient of variation (CV) provide the measurement uncertainty estimate required, if the QC process includes all the steps and components involved in examining patient samples or QC materials behave like patient samples. These data are best collected over time across as many routine-operating conditions as possible to provide the most reliable estimate of measurement uncertainty. For established methods collect at least 6 months worth of internal QC data to calculate SD or CV. It is important that data are collected during a sufficiently long period of time to ensure that the data encompass as many routine changes of conditions as possible, eg, recalibrations, replenishment of reagents (same lot), routine instrument maintenance, lot changes of calibrators and reagents, and different operators. For new methods use at least 30 data points for each level of QC using at least 2 different lots of calibrator and reagents, where applicable. This provides a short-term measurement uncertainty. Continue to evaluate until the long term can be established. In general, the more data collected, the more reliable the estimate.

However, collecting results from samples in succession over several runs over a short period of time

may lead to overestimating the measurement uncertainty if undue systematic effects occur. On the other hand, recalculating the uncertainty of quality control results at too frequent intervals may result in underestimating the characteristic long-term uncertainty of the measurement by eliminating the between-run component of variation. Underestimation of uncertainty may also arise with excessive trimming of the dataset. Any trimming of the dataset should be carefully justified. It is so crucial that a representative sample of QC data is used for the estimation of measurement uncertainty. it is the responsibility of laboratory director to ensure sound quality control data sets are used in measurement uncertainty estimation

External quality assurance data or proficiency testing should not be used for estimation of measurement of uncertainty unless the material is intended to serve this purpose. However, it can be used to estimate bias if fit for that purpose such as using commutable material with metrologically traceable value.

Measurement uncertainty can be reported as an absolute value or percentage. If considered over a wide measuring interval, it is often appropriate to quote the uncertainty as a relative uncertainty, u(x)/|x| or %u(x), whereas at low concentrations or within narrow intervals, it is usually better to quote the uncertainty as an absolute value, u(x).

The numerical value of a measurement (x); its standard uncertainty, uc(x); or its expanded uncertainty U(x), should not be given with an excessive number of digits. It usually suffices to quote uc(x) and U(x) to, at most, two significant digits unless otherwise indicated. In reporting final results, it is generally better to round uncertainties up rather than to the nearest digit. The measurement value should be stated to be consistent with its uncertainty. For example, if x = 48.261 mg with U(x) = 1.2 mg, x should be rounded to 48.3 mg; if U(x) = 1 mg, x should be rounded to 48 mg.

5. Bias Assessment

Bias is the numerical expression of trueness, as imprecision is the numerical expression of precision. Any estimate of the value of a bias is inevitably uncertain; therefore, correcting a measured value for this bias adds to the combined uncertainty. Correcting for known bias will therefore improve the trueness of a reported result, but increase the uncertainty.

When a bias is determined and found to be small relative to the uncertainty of the uncorrected measurement, it is not necessary to correct the measurement result for the bias because it will not make a material difference to the coverage interval of the result. Furthermore, any bias correction that is insignificant relative to the clinical utility of the result adds little or no value.

Should a bias be determined that is significant relative to the uncertainty of the uncorrected

measurement or to clinical utility, it may indicate that the measurement system is out of calibration or is otherwise producing invalid results and corrective actions are required.

Any modification of a measurement system's standard calibration protocol needs to be fully documented and validated.

When the root cause of a bias cannot be determined or eliminated, methods have been proposed for expanding the uncertainty interval to cover the bias

From a formal metrological point of view, calibration using a commutable reference material with an assigned value and stated uncertainty and traceability provides the most direct correction for bias. In practice, however, the results of a measurement are influenced by many factors that many calibrators do not fully address.

6. Unsatisfactory results

Measurement uncertainty estimation should be evaluated for its fitness for clinical utility or measurement specifications. The calculated Measurement uncertainty should be evaluated to determine the significance of the measurand in impacting patient care. That is, if a patient result at the lower end of the uncertainty range would lead to a different clinical decision than a result at the upper end of the range, the uncertainty is too large.

If the uncertainty estimated by the top-down method for a particular measurement procedure is not within that expected by the specifications of the measurement procedure or does not meet the needs for the intended use of the results, a systematic review of the uncertainty sources and components is necessary. The bottom-up procedure offers such a structured approach for measurement systems when the component sub-processes can be individually characterized. If the uncertainty estimated by the top-down method exceeds the estimate from the bottom-up method, the user should review the measurement model and components of the bottom-up method for missing or underestimated components.

The medical laboratory must define actions it will take when examinations with Measurement uncertainty estimates are not functioning within a state of statistical control. This includes root cause analysis and subsequent corrective action. This corrective action should consist of how the examination will be again monitored to ensure statistical control. This action should also include how problems with the Measurement uncertainty estimate will be communicated. This action should also include how the new Measurement uncertainty estimate will be re-established, documented, and communicated after statistical control is again achieved.

The medical laboratory must define how it will communicate and document changes in the estimate of UM when imprecision actually improves, with regard to a smaller standard deviation or coefficient of variation.

7. Re-estimating Uncertainty

Laboratories are required to re-estimate measurement uncertainty only when changes to their operations are made that may affect sources of uncertainty and these sources have not been shown to be unaffected through method validation or other studies.

8. References and Further reading

- INTERNATIONAL STANDARD ISO 15189 Third edition 2012-11-01
- CAP 15189 Program - Measurement Uncertainty Guideline for Laboratories Working Document
- CLSI EP29-A: Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline
- Requirements For The Estimation Of Measurement Uncertainty, National Pathology Accreditation Advisory Council 2007 Australia
- Policy on Estimating Measurement Uncertainty for ISO 15189 Testing Laboratories, American Association for Laboratory Accreditation 2014