

Traceability and Uncertainty of Measurement for Medical Laboratories—OLA's Expectations

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INTRODUCTION

As an accrediting body, the Quality Management Program—Laboratory Services' (QMP-LS) Ontario Laboratory Accreditation (OLA) division must ensure that accredited laboratories meet standards of traceability and uncertainty of measurement.^{1,2}

The purpose of this article is to provide interpretive guidance for diagnostic medical laboratories accredited by QMP-LS. It offers:

- definitions;
- an explanation of traceability and uncertainty of measurement concepts;
- clarification on what OLA requires; and
- tips on estimating uncertainty of measurement.

Following publication, this information will be incorporated into the OLA Program Information available on the QMP-LS Web site and QView™ (QMP-LS' password-protected document server).

DEFINITIONS

Traceability (Tr) – Property of the result of a measurement or value of a standard whereby it can be related to stated references (usually national or international standards) through an unbroken chain of comparisons all having stated uncertainties. Source: Standards Council of Canada CAN-P-1626 *Policy on traceability requirements for calibration sources used by accredited testing laboratories*.³

Uncertainty of Measurement (UM) – Parameter, associated with the result of measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand (the quantity intended to be measured). Source: National Pathology Accreditation Advisory Council *Requirements for the estimation of measurement uncertainty*.⁴

CONCEPTS OF TRACEABILITY AND UNCERTAINTY OF MEASUREMENT

Ensuring that laboratory measurements are valid requires the use of appropriate reference materials for method validation, calibration, traceability, estimation of uncertainty, and quality control/quality assurance. For medical laboratory testing, Tr and UM are essential and usually overlapping components of the process as illustrated in Figure 1 (adapted from Alan Squirrell's *Confidence in measurements*).⁵



*Mediocrity is the result
when fear of failure
permeates an organization.*

~William W. Scherkenbach

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Traceability and Uncertainty of Measurement for Medical Laboratories—OLA's Expectations

The long-term clinical goal (sometimes referred to as “fitness for clinical purpose”) is to meaningfully compare test results produced by any laboratory at any time.

Traceability is characterized by six sub-components:

1. An unbroken chain of comparisons going back to an acceptable national or international set of references
2. Uncertainty of measurement (calculated or estimated for each step in the chain by agreed methods and stated as such to allow overall uncertainty to be calculated or estimated for the entire process)
3. Documentation
4. Competence (evidence of technical competence)
5. Reference to SI Units (where possible, chain of comparisons must end with reference to primary standards that are traceable to SI units)
6. Calibration intervals (length, number of variables, uncertainty required, frequency of use, etc.)

Merely stating that results are obtained against a manufacturer's reference material or that the method is standardized against a standard/reference available from a reference body is not sufficient to ensure traceability of results.

Uncertainty of Measurement (UM) provides quantitative estimates of the level of confidence that a laboratory has in its analytical precision of test results. Thus, imprecision is included in estimates of the UM. Another component of the analytical process that is associated with UM is bias, which is the trueness or closeness (accuracy) of the results to expected or assigned values.

Uncertainty of measurement concepts assume no bias. However, if bias is present or corrected for, then it should be combined with UM to provide estimates of the overall uncertainty.

For more details on UM, refer to Standards Council of Canada's CAN-P-1623 *PALCAN Interpretation and guidance on the estimation of uncertainty of measurement in testing* and the Australian National Pathology Accreditation Advisory Council's *Requirements for the estimation of measurement uncertainty*.^{6,4}

OLA REQUIREMENTS FOR TRACEABILITY AND UNCERTAINTY OF MEASUREMENT

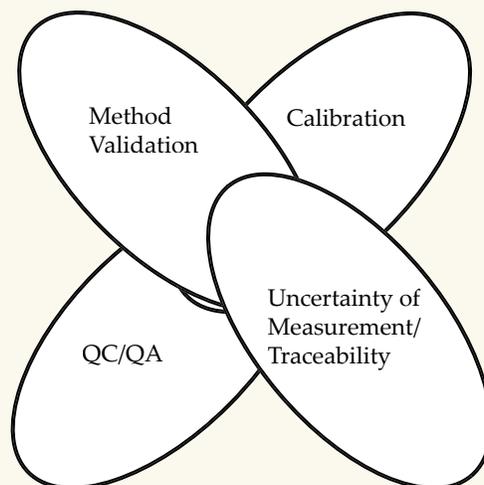
OLA's accreditation scheme is based on ISO 15189:2003 *Medical laboratories—particular requirements for quality and competence* (CAN/CSA Z15189-03) and ISO/IEC 17011:2004 *Conformity assessment—General requirements for accreditation bodies accrediting conformity assessment bodies*.^{1,2} OLA strives to provide requirements that are concise and accompanying guidance information that assists laboratories in the application of requirements.

Current OLA requirements do not provide adequate information on uncertainty of measurement to medical laboratories. Thus in the revised version of the requirements, scheduled for release later this year, OLA will change its requirements as shown in Table 1.

TIPS ON ESTIMATING AND REPORTING UNCERTAINTY OF MEASUREMENT

Most of the available information at the national and international level relates to calibration laboratories and/or calibration processes that are required to meet the accreditation standard ISO/IEC 17025:2005 *General requirements for the competence of calibration and testing laboratories*.⁷ Traditionally, the authoritative reference is the *Guide to the Expression of*

Figure 1. Overlapping functions associated with valid measurements



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Uncertainty in Measurement (GUM).⁸ This comprehensive guide is widely cited in the fields of analytical chemistry and physical testing but it does not address unique aspects of medical testing. Uncertainty of measurement (UM) is relatively new to the medical laboratory. Australia's National Pathology Accreditation Advisory Council recently published its *Requirements for the estimation of measurement uncertainty*, which offers a practical guide for implementation of UM in medical laboratories.⁴ The American Association for Laboratory Accreditation (A2LA) in the United States recently circulated a draft UM policy for medical laboratories, but it is not yet widely available. For Ontario's medical laboratories, here are some practical tips on estimating and reporting UM.

Uncertainty of measurement (UM) represents the expected variability in a laboratory result if the test is repeated a second time. Hence it is a measure of precision and is reported in standard deviation (SD) units or relative SD expressed as the coefficient of variation (CV) or % CV. The QMP-LS External Quality Assessment (EQA) Broadsheet – *Precision Goals in Clinical Chemistry* outlines the procedure to determine imprecision.⁹ In order to determine if repeat results are measurably different, a confidence level is applied to UM data. For example, a 95% confidence level is generally applied to numerical results such that a difference $>2.5 \times 1.96 \text{ SD (UM)}$ or $>2.77 \times \text{CV}$ constitutes a measurable difference.

Uncertainty of measurement (UM) is classified as standard uncertainty type A (evaluations by statistical methods such as those used in determining imprecision), standard uncertainty type B (evaluations by other methods), and expanded uncertainty. Type A standard uncertainty is the standard deviation of the mean of replica measurements, also known as the standard error of the mean (SEM). Type B standard uncertainty is the uncertainty obtained by dividing all listed uncertainties by a weighted factor (multiplier) based on the distribution (e.g. normal, rectangular, triangular). A typical type B evaluation is to compute the arithmetic mean and SD of several observations and determine the experimental SD of the mean, also termed the SD of the mean or formerly called the standard error of the mean (SEM). As previously

Table 1. Changes to OLA Requirements Expected with Version 4

Requirement No.	Text
IV.8.3 on Traceability to move to VII.14	<p><i>All calibration material shall be traceable to an accepted reference standard that is expressed in SI units whenever possible. The laboratory shall have a mechanism to ensure accuracy if the information is not available from the manufacturer.</i></p> <p>“What to Look for” (WTLF) Guidance to change from: <i>Is there evidence that calibrators are traceable to an accepted reference standard?</i> By replacing with the following (which is very similar to ISO 15189, clause 5.6.3): <i>Has a program for calibration of measuring systems and verification of trueness been designed and performed to ensure that results are traceable to SI units or by reference to a natural constant or other stated reference (e.g. calibrators traceable to an accepted reference standard)? Where traceability to a reference preparation is not possible or relevant, have other means for providing confidence in the results been applied?</i></p> <p>Examples:</p> <ul style="list-style-type: none"> • Participation in inter-laboratory comparisons • Use of suitable reference materials, certified to indicate the characterization of the material • Examination or calibration by another procedure • Ratio or reciprocity-type measurements • Mutual consent standards or methods that are clearly established, specified, characterized and mutually agreed upon • Documentation of statements regarding reagents, procedures or the examination system when traceability is provided by the supplier or manufacturer.
VI.8 on Uncertainty of Measurement	<p>Requirement to be re-worded as follows: <i>The laboratory shall determine the uncertainty of results, where relevant and possible. Potential sources of error or limiting factors (e.g. sample preparation, calibrators, reference materials, methods, equipment, environmental conditions, sample condition, operator) shall be taken into account.</i></p> <p>The existing WTLF Guidance: <i>Have potential sources of error or limiting factors been determined where relevant or possible?</i></p> <p>Will be augmented with: <i>For quantitative measurements, has an estimate of uncertainty been established?</i></p>

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indicated, UM assumes no bias exists, however, when information on bias and biological variation are available, they must be included in the estimates of overall UM. Expanded uncertainty is the combined uncertainty (type A & B) multiplied by a coverage factor (k-value) that normally represents the confidence level associated with a normal distribution (k=2 representing a confidence level of 95%). For further information on biological variation, consult Dr. James Westgard's Web page at <http://www.westgard.com/biodatabase1.htm>, or Dr. Callum Fraser's textbook on intra-individual variation titled *Biological Variation: From Principles to Practice*.^{10,11}

As mentioned in the previous paragraph, a combined or expanded estimate of UM sometimes must be determined. In this case a typical approach to calculate or estimate UM is as follows:

- Identify the measurand
- Determine calibrator uncertainty
- Set analytical goal (based on biological variation)
- Identify all measurement uncertainties
 - Imprecision
 - Bias
 - Calibrator uncertainty
- Calculate combined uncertainty
- Calculate expanded uncertainty (combined uncertainty × k-value). Expanded uncertainty provides a high level of confidence by applying a coverage factor (k-value) in the calculation. This k-value represents a coverage probability based on normal distribution. For a detailed explanation of the k-value, refer to Dr. Westgard's Web page or the UKAS (United Kingdom) M3003 *The Expression of Uncertainty and Confidence in Measurement*.^{10,12}

When reporting the UM for clinical purposes as a % CV, the goal is to demonstrate the preciseness in the method even though inherent biological variation may exist. This helps to achieve the long-term goal to meaningfully compare test results produced by any laboratory at any time. A typical reporting format is one in which the UM % CV reported takes into account any combined uncertainty resulting from biological variation and represents any expanded uncertainty (coverage probability based on normal distribution).

SUMMARY

As an accrediting body, QMP-LS/OLA must ensure that accredited laboratories meet standards of traceability (Tr) and uncertainty of measurement (UM). These functions ensure valid laboratory measurements, in concert with method validation, quality control and quality assurance. While the concept of traceability (Tr) through calibration is well understood within medical laboratories, the concept of uncertainty of measurement (UM) is not. OLA's accreditation requirements (Version 3, September 2005) are not altogether clear on these subjects, and will be revised/clarified with the release of Version 4 (anticipated in January 2008).

The laboratory's long-term goal in estimating and reporting uncertainty of measurement is to demonstrate the preciseness in its method (determine if repeat results are measurably different) recognizing that inherent biological variation may exist and accounting for probability based on normal distribution. This allows for a meaningful comparison of test results produced by any laboratory at any time.

Estimating and reporting the uncertainty of measurement (UM) is required of laboratories accredited to ISO/IEC 15189: 2003 *Medical laboratories—Particular requirements for quality and competence*. Unfortunately, this concept is relatively new to medical laboratories and few resources are available that relate specifically to medical laboratories. The estimated uncertainty of measurement (UM) can be reported as the % CV (relative SD) to which biological variation and a confidence level (coverage probability based on normal distribution) have been applied.

Information contained in this article will be incorporated into program information publicly available on the QMP-LS Web site and to participating laboratories via QView™.

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QMP-LS External Quality Assessment Educational Committee Comments

The College of Medical Laboratory Technologists of Ontario's (CMLTO) Quality Assurance Committee has approved the addition of "External Proficiency Committee Comments or Broadsheets" to the Review and Reading section of the Option A: Self-directed Study Guidelines to count towards Professional Portfolio hours. Starting mid-September the forms will be available on-line (http://www.cmlto.com/quality_assurance/professional_portfolio/).

Dr. Pui-Yuen Wong Receives The Carl R. Joliff Award for Lifetime Achievement in Clinical or Diagnostic Immunology

QMP-LS congratulates Dr. Pui-Yuen Wong on receiving The Carl R. Joliff Award for Lifetime Achievement in Clinical or Diagnostic Immunology. Dr. Wong received this award in July at the American Association for Clinical Chemistry (AACC) meeting. This award recognizes outstanding contributions in service or education in the area of immunology or immunodiagnosics. Congratulations Dr. Wong!

Clinical Laboratory Management Association (CLMA) Trillium Chapter Workshops

The CLMA, in partnership with Abbott, presents: Two SmartLab workshops in one day! 1) *Improving Patient Safety from The Laboratory* and, 2) *Align New Leaders with Succession Management*.

When? Friday, October 26, 2007

Where? Burlington Convention Centre, Burloak Drive

Early registration including payment by October 5, 2007:

Workshop fee for CLMA member \$150

Workshop fee for non-members \$220 (limited quantity)

For more information go to http://www.qmpls.org/pub_resources/publications/qmpls_news/html/issue_118/CLMA_26%20October%202007_BCC%20Smartlab_brochure-O.pdf or contact Maureen by e-mail: maureen.macdonald@sickkids.ca.

Safety Inspections vs. Safety Audits



There are two requirements within the safety section of the OLA requirements (Version 3, September 2005) that relate to safety audits and safety inspections.

X.A.3: "The safety program shall be regularly audited within the organization and reviewed by laboratory management annually."

X.A.4: "Work areas shall be surveyed or inspected at least annually by the safety officer and/or safety committee."

Safety audits and safety inspections are two distinct activities.

Safety Audit: The requirement for an annual safety "audit" is most accurately referenced to the National Standard of Canada titled *CAN/CSA-Z15190-05: Medical laboratories – Requirements for safety*. This activity is not a physical inspection of workplace conditions by a worker representative, but is instead an annual review of the entire safety program and its documents and records by the Joint Health and Safety Committee (JHSC) or laboratory management. It should include:

1. A review of the entire contents of the safety manual including all safety-related policies and procedures such as hand washing, the use of sharps, standard precautions, handling of waste and the use of personal protective equipment.
2. A review of the status of staff education and training, particularly the status of Workplace Hazardous Materials Information System (WHMIS) and Transportation of Dangerous Goods Certifications.
3. A look-back at the past year's safety inspections and the outcomes from those inspections.
4. A check that the hazardous materials inventory is accurate and that exposure is controlled.
5. A review of first aid services, health surveillance practices and first aid equipment.
6. A look-back at accident and illness investigations and the protocol for exposure to chemicals and biohazards.
7. A review of the Joint Health and Safety Committee (JHSC) membership.
8. A review of any other safety-related programs.

OLA assessors will look for evidence that an annual safety audit is conducted. The results of both the regular safety inspections and the annual safety audit must be recorded, including any actions taken as a result of either activity.

Safety Inspection: Regular and documented safety inspections are required under the Ontario Occupational Health and Safety Act. The Act requires the JHSC to choose one worker (not a managerial employee) representative from their group to inspect the workplace. This responsibility can be rotated among the worker representatives. The workplace should be inspected at least once a month. However, the Act specifies that if the workplace is too large to be inspected fully each month, the committee can establish an inspection schedule that will ensure at least part of the workplace is inspected each month and the entire workplace is inspected at least once a year. Thus, the OLA requirement states that the inspections shall be conducted at least annually. Our observation is that most laboratories conduct a monthly inspection.

The committee member who performs the inspection must report back to the JHSC to inform them of any hazards to workers. The committee must react to the inspection results within a reasonable time and may make recommendations to the employer. Under the Act, the employer is required to respond to the recommendations within 21 days.

Ensuring the safety of patients and employees is more than a moral obligation of laboratory management—it is the law. Accordingly, OLA will continue to assess compliance with these safety requirements for accreditation.

QMP-LS Affiliated International Laboratory Accreditation Cooperation Celebrates Its 30th Anniversary

The International Laboratory Accreditation Cooperation (ILAC) was formed in 1977 and this year celebrates its 30th anniversary. ILAC is the international cooperation of laboratory and inspection accreditation bodies. QMP-LS has been a member since 2002, and currently enjoys affiliate status. One of the primary aims of ILAC is the removal of technical barriers to trade, through promotion of accreditation using international standards such as ISO 15189 *Medical laboratories – Particular requirements for quality and competence*. ILAC guides have been invaluable in the development of Ontario Laboratory Accreditation (OLA), providing the foundation for assessor training and guidance on protocols for surveillance of proficiency testing/external quality assessment in accredited laboratories. The Director, OLA is a member of both the Accreditation Issues Committee and the Proficiency Testing Consultative Group, and serves ILAC as the official liaison between these two. These activities give QMP-LS access to a network of individuals whose experience in accreditation and proficiency testing/external quality assessment provides valuable insight. A total of 58 signatories representing 46 economies have now signed the ILAC Mutual Recognition Arrangement, enhancing the acceptance of products and services across national borders. In Canada, the Standards Council of Canada and the Canadian Association of Environmental Analytical Laboratories are signatories and thus full members of ILAC. QMP-LS is fortunate to have affiliations with both of these organizations. It joins the international laboratory community in congratulating ILAC on its 30-year anniversary.