DIAGNOSTIC ACCREDITATION PROGRAM
College of Physicians and Surgeons of British Columbia
300–669 Howe Street
Vancouver BC V6C 0B4
www.cpsbc.ca
Telephone: 604-733-7758 ext. 2635
Toll Free: 1-800-461-3008 (in BC)
Fax: 604-733-3503

Guide to Fulfillment of Measurement Uncertainty

Purpose

This document from the Diagnostic Accreditation Program (DAP) provides guidance for organizations on fulfilling the Laboratory Medicine Accreditation Standards.

If you have questions related to the standards please email them to: laboratorymedicine@cpsbc.ca

Terms and definitions

accuracy	The closeness of agreement between a measured quantity value and the true quantity value of the measurand.	VIM[1]
bias	An estimate of systematic measurement error.	VIM
examination	A set of operations having the object of determining the value or characteristics of a property. Synonyms: analysis, assessment, investigation, measurement, study, test	ISO
imprecision	An expressed variation, either standard deviation or coefficient of variation, calculated from the results in a set of replicate measurements.	
interference	In laboratory medicine and clinical chemistry, a cause of clinically significant bias in the measured analyte concentration due to the effect of another component or property of the sample.	CLSI
measurand	Quantity intended to be measured. Synonym: analyte	ISO
measurement uncertainty (MU)	A non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand based on the method used.	CLSI

[1] International Organization for Standardization, International Vocabulary of Basic and General Terms in Metrology. Geneva: International Organization for Standardization; Geneva, Switzerland1993.

metrological traceability	The property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to measurement uncertainty.	CLSI
procedure	A documented, specified way to carry out an activity of a process. **Note:** For the purposes of accreditation, procedures must always be documented, implemented and maintained.	ISO
process	A set of interrelated or interacting activities which transform inputs into outputs.	ISO
sample	A discrete portion of a body fluid, breath, hair or tissue taken for examination of one or more quantities or properties assumed to apply for the whole. One or more parts taken from a primary sample. Synonyms: specimen, primary sample, aliquot	ISO
user (of laboratory services)	Physicians and others who order diagnostic examinations and/or receive diagnostic information and reports from laboratories. Synonyms: authorized requestor, ordering physician, clinical personnel	DAP

Introduction

The DAP accreditation process assesses the measurement uncertainty at the regional level. Incorporation of ISO 15189 requirements into the DAP laboratory medicine standards requires health authorities and organizations to ensure measurement uncertainty of laboratory results to be established for all quantitative measurands at their sites. This document is intended to provide an introduction to measurement uncertainty (MU) in the clinical laboratory.

Objectives

The objectives of this document are to:

- familiarize assessors with the concept of MU
- introduce approaches laboratories can use to develop MU estimates
- describe the assessment of MU

What is measurement uncertainty?

In laboratory examination, the concept of error is widely accepted to set quality goals, for example, total allowable error or allowable limit of error. It is important to note that this approach may overestimate the error and thus the concept of measurement uncertainty (MU) evolved. The definition of MU, taken from the current *Guide to the Expression of Uncertainty in Measurement (GUM)*, is “a parameter

associated with the result of a measurement that characterizes the dispersion of the values that could reasonably be attributed to the measurand." The parameter may be considered as a standard deviation, a range, or an interval with a certain level of confidence. An estimate of MU provides an interval or range of values within which the true value is believed to lie with an approximate confidence level of 95%.

Total error (TE) versus MU

All laboratory examination results reported out in numerical values are imperfect and have many potential sources of variation. When a sample is repeatedly examined, there will be some variation or imprecision in the results. Imprecision can be estimated by measuring quality control (QC) materials. It is important that data from internal QC are collected over a sufficient period of time to ensure that the data encompass as many routine changes in conditions as possible (e.g. recalibrations, replenishment of the same lot of reagents, routine maintenance, lot changes of calibrators and reagents and different operators). The dispersion of results obtained from this data is comparative to a Gaussian (normal distribution) curve, which can be statistically quantified as a standard deviation (SD) from the mean.

TE concept describes the total error of the measuring system and comprises of two main components:

1. Random error refers to the random scatter or imprecision of repeated measurements. The imprecision data obtained from routine monitoring of internal quality control can be used to perform a quantitative estimate of the measurement uncertainty for a particular measurand.
2. Systematic error or bias is the difference between the mean of the measured values and the assumed true value. Bias from components associated with corrections and reference standards or calibrators can contribute to the uncertainty. The source of uncertainty associated with the numerical value of the measurand present in the calibrator can be estimated by the commercial supplier of the calibrator or by the laboratory if the calibrator has been prepared in-house.

TE is a measurement of bias +1.65 SD, where 1.65 represents approximately 95% dispersion of results obtained from one side of the imprecision Gaussian curve. It is useful in calculating and setting an acceptable upper limit of TE for measurement results. TE does not apply to individual patient results that could have a different imprecision from the 1.65 SD.

Contrary to the TE concept, MU does not estimate error in a measurement but provides an interval or range of values within which the true value is believed to lie within a stated level of confidence.

In a laboratory measurement system, the combined effect of the individual sources of variability on measurement results is adequately reflected in the dispersion of results obtained from QC samples. Since patient results are compared to each other and with reference values over time, to calculate MU, it is appropriate to use QC data obtained over a period of time to capture variability due to routine changes in the measuring system.

During routine changes in conditions, both large and small shifts may be attributed to systematic errors. If the shift is large, it may require intervention such as recalibration to eliminate or minimize the bias. However, when shifts are viewed over a long period of time, it may be regarded as random variation attributable to ongoing routine changes of conditions rather than bias. In MU measurement, known bias is eliminated or minimized. If a bias value has been estimated, the uncertainty of the value used for bias correction has to be considered in the overall MU calculation.

The basic parameter of MU is 1 SD. Because the SD of the QC reflects the combined effect of all the individual uncertainties in the measurement system, the SD can be considered as the combined standard uncertainty for patient results around the mean value of a particular QC. Since 1 SD covers

approximately 68% of the dispersion of QC values, applying a coverage factor of 2 to provide an expanded MU widens the uncertainty to a more useful coverage of 95%. Therefore, assuming the dispersion of QC values applies to patient results, MU can be calculated as +2 SD (95% confidence) of the measured patient result. If several levels of QC are used then MU should be calculated for each and a decision is made as to whether to include the uncertainty for each QC level.

MU considers a single measurement result to be the best estimate of a true value and it is centered on the dispersion of other values that have been obtained if the measurement had been repeated with a 95% confidence. It is important to note that MU is concerned only with analytical and not physiological variability therefore it does not consider or incorporate biological variation.

How do laboratories determine the measurement uncertainty?

There are two common types of approach to determine the measurement uncertainty; a bottom-up approach as per the *Guide to the Expression of Uncertainty in Measurement (GUM)* principles and a top-down approach using examination performance information.

1. The GUM bottom-up approach to estimating MU, identifies all potential sources of uncertainty such as calibration, pipetting, weighing, temperature and instrument fluctuations and attributing to each an uncertainty estimate as a standard deviation obtained by experiment (Type A) or from available information (Type B). Type A estimate is based on statistical analysis. Type B is obtained by means other than statistical analysis such as past experiences or studies on related measuring systems, manufacturer's data, literature, or professional judgement. The contributing uncertainties are combined in a comprehensive mathematical model of the MU to provide an expanded uncertainty associated with the specific result.
2. The top-down approach to estimating MU uses the whole method performance to include the effects from as many relevant uncertainty sources as possible using the method bias (systematic errors) and precision data (random errors). This approach uses data from ongoing intra-laboratory quality control checks, method validation, and/or proficiency testing to calculate estimates of the standard uncertainty associated with the result produced by the overall testing procedure or method. The data used should be collected over a long period of time to ensure that the data encompasses as many routine changes of conditions as possible.

Laboratories may use various combinations and or modifications of the GUM bottom-up approach and the top-down approach, personal experience and information on certified reference methods and materials to determine the measurement uncertainty.

Why must laboratories calculate measurement uncertainty?

Laboratories are responsible for ensuring that examination results are fit for their clinical purpose.

Calculating measurement uncertainty may assist in determining the confidence that can be placed in an examination result and defining where an examination may be improved.

Incorporation of ISO 15189 into the laboratory medicine accreditations standards requires laboratories to address MU for quantitative laboratory examinations. It is preferable but not mandatory to calculate MU on semi-quantitative examinations.

MU is an important consideration in the comparability of examination results.

MU is an essential component for achieving standardized and harmonized measurement results through metrological traceability.

Assessment of measurement uncertainty

All of the criteria associated with measurement uncertainty are only assessed at the regional level.

DAP measurement uncertainty requirements

There are six criteria used to evaluate the laboratory's measurement uncertainty. They are as follows:

EXA3.2.1	**M**	The laboratory determines measurement uncertainty for each quantitative measurement procedure.
Evidence:		Laboratories: • Will be asked about quantitative examinations where measurement uncertainty has been calculated • Will provide and discuss the procedures used to calculate measurement uncertainty and any associated performance requirements
Where:		Regional assessment
Comment:		Laboratories may use the following determinations of MU: • A bottom-up approach as per GUM principles • A top-down approach using examination performance information • Other approaches using a combination or modifications of the above • An online measurement uncertainty calculator It is not necessary for laboratories to have measurement uncertainty calculated for semi-quantitative measurands. The laboratory should have calculated measurement uncertainty for all quantitative measurands.

EXA3.2.2	**M**	The performance requirements for measurement uncertainty for each quantitative measurement procedure are defined.
Evidence:		Documented performance requirements for measurement uncertainty such as: • The analytical goal for precision of an examination method should remain below half the intra-individual biological variation • Collective uncertainty should not exceed 25% of the maximum calculated standard deviation for an examination
Where:		Regional assessment
Comment:		Laboratories shall establish performance requirements for measurement uncertainty. These may include internationally accepted performance goals, establishing analytical goals for imprecision based on intra-individual biological variation or defining upper limits as a proportion of the intra-individual biological variation of the measurand.

EXA3.2.3	**M**	Estimation of measurement uncertainty is reviewed at a defined frequency. This is documented. *Guidance: Estimation of measurement uncertainty does not require reassessment unless the original conditions of estimation have changed.*
Evidence:		Where the laboratory has defined a time frame for the review of measurement uncertainty, the assessors will require evidence that this has been done.
Where:		Regional/organizational assessment
Comment:		The laboratory must review measurement uncertainty within any defined timeframes. If the uncertainty estimated for a particular measurand is not within specified expectations or the uncertainty does not meet the requirements for the intended use of the results, a systematic review of uncertainty sources and components is required.

EXA3.2.4	**M**	Measurement uncertainty is considered when interpreting measured quantitative values.
Evidence:		Records demonstrating the provision or discussion of measurement uncertainty to users.
Where:		Regional assessment
Interpretation:		By making measurement uncertainty information available to users, laboratories can contribute to improved interpretation of patient results because such data is essential for rational comparison of results with clinical decision limits and previous patient results.

EXA3.2.5	**M**	Measurement uncertainty is provided to users upon request.
Evidence:		Records demonstrating the provision or discussion of measurement uncertainty to users.
Where:		Regional assessment
Interpretation:		Laboratories must be prepared to stipulate a clinically relevant timeframe for the estimation of measurement uncertainty upon request. Laboratories must be able to articulate for the assessor how the measurement uncertainty would be calculated.

EXA3.2.6	Where examinations include a measurement step but do not report a quantitative value, the laboratory calculates the measurement uncertainty where it has value in assessing the reliability of the examination procedure or has influence of the reported result (e.g. serology testing for immune status).
Evidence:	Records indicating a review of the calculation of measurement uncertainty in these examinations.
Where:	Regional assessment
Interpretation:	This is a non-mandatory requirement. However, laboratories may choose to calculate measurement uncertainty for this type of result (e.g. FIT examinations).

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