	<i>The American Association for Laboratory Accreditation</i>	
	P603e: Annex- Policy on Estimating Measurement Uncertainty for Medical Testing Laboratories	Document Issued: November 6, 2009
		Page 1 of 11

A2LA has compiled information for classifying some common types of test methods according to the *P103-A2LA Policy on Estimating Measurement Uncertainty in Testing Laboratories*. This A2LA Annex is intended as a means to facilitate transition to compliance with ISO 15189, and is subject to change as additional guidance is made available internationally.

This guidance has been developed and reviewed by the A2LA Medical Testing Technical Advisory Committee, provides information about how to categorize methods typically categorized. The medical laboratory must comply with 5.6.2 and 5.6.3 of ISO 15189 regardless of whether a method is listed below in Category 1 or 2 (see Section 3).

1.0 Introduction

Uncertainty of Measurement (UM) in medical laboratory testing is the doubt associated with what represents the trueness of a medical laboratory test result. ISO 15189 (3.19) defines UM as:

“...a parameter associated with the result of a measurement that characterizes the dispersion of values that could be reasonably attributed to the measurand.”


(Measurand is the quantified property of the analyte of interest in the test system, whereas analyte is an informal term used to identify the substance being measured.)

Indeed, virtually all test results are provided to a practitioner and/or patient without any indication to either party of the certainty of that measurement. For example, if today’s glucose value is 110 mg/dl, and tomorrow’s is 112 mg/dl, the question remains, “Are these results different?” On the surface, yes, these results appear different; in fact, one is considered a “normal” value, while the other is considered “abnormal.” However, without understanding the variation inherent in the process used to measure glucose, such a judgment cannot be made. This variation contributes to the uncertainty of the measured value. Thus, understanding UM allows a practitioner to understand the probability of trueness of that value, subsequently leading to a better understanding of the clinical condition of that patient. Thus, to maximize the clinician’s ability to effectively manage patient care, communication between the laboratory and the clinician regarding UM is desirable.

Medical Laboratories need Uncertainty of Measurement.

Uncertainty of Measurement ultimately allows a practitioner better understanding of the clinical significance of a value, contributing to better clinical care of the patient.

- By understanding the amount of uncertainty in a measurement, a clinician can better understand the fitness of use of that measurement for clinical purposes.
- By controlling UM for applicable methods, laboratories can have assurance of the accuracy where accuracy represents both precision and trueness of their chosen methods.

	<i>The American Association for Laboratory Accreditation</i>	
	P603e: Annex- Policy on Estimating Measurement Uncertainty for Medical Testing Laboratories	Document Issued: November 6, 2009
		Page 2 of 11

By understanding UM, the clinician can understand the difference between normal process variation and variation that cannot be accounted for in the testing process. For example, UM does not account for instances where a wrong patient was drawn and the subsequent analytical value is inconsistent with that patient's history.

Additionally, ISO 15189 (5.6.2) requires that:

“The laboratory shall determine the uncertainty of results, where relevant and possible.”

There are 2 sources of uncertainty that contribute to UM in the Medical Laboratory.

There is uncertainty associated with the calibrators used in the laboratory methods.

- For example, a calibrator might indicate a value of 100 mg/dl; however, the manufacturer might state a level of uncertainty for that measurement.
- If the manufacturer does not estimate uncertainty for its calibrator, the laboratory must do this by conducting another uncertainty of measurement for the calibrator.

There is also uncertainty derived from the common cause variation (random error) associated with repetitive testing of the same sample in the test system.

- This common cause variation is also called “imprecision.”
- These data are generally obtained from internal quality control data.

Refer to the Section “Identify the Components of UM” below for the management of these sources.

A number of contributors influence the value of the UM.

Thus the collection of data to estimate UM should include testing with different operators at different times with different pieces of equipment, for example.

Terms Associated with Uncertainty of Measurement

Accuracy


Closeness of a measured value to the true value of the measurand.

Analyte

The substance measured from a sample. The characteristic of the substance that is measured is called the measurand, defined below.

Target Uncertainty

Generally accepted target uncertainty of an analytical method. One widely used method to determine Target Uncertainty is to define the upper acceptable limit for imprecision as a proportion

	<i>The American Association for Laboratory Accreditation</i>	
	P603e: Annex- Policy on Estimating Measurement Uncertainty for Medical Testing Laboratories	Document Issued: November 6, 2009
		Page 3 of 11

of the intra-individual biological variation of the analyte. This concept is sometimes referred to as analytical goal.

Bias

Analytic error of a test system as determined by repetitive measurements of sample measurand in contrast to the true value of the measurand.

Error

Difference between the measured value of the measurand and the true value of the measurand.

Examinations

Clinical Tests performed in the Medical Laboratory.

Imprecision

Expressed variation, either standard deviation or coefficient of variation, calculated from the results in a set of replicate measurements.

Inaccuracy

See Bias.

Measurand

Characteristic of a substance that is measured.

Numerical Significance

Figures of a number that have practical meaning. The number of significant figures used in a measurement expresses the degree of precision of the measuring system.

Precision

The closeness of expressed variation, either standard deviation or coefficient of variation, calculated from the results in a set of replicate measurements.

Proficiency Testing

Inter-laboratory comparisons used to monitor performance of a laboratory with regard to individual tests, measurements, or observations. Also called “external quality assurance” (EQA) in many settings

Standard International Units (SI)

The system of metric units that is adopted by all major countries for use in science, medicine, industry, and commerce. It encompasses such characteristics as:

- Length (m)
- Mass (kg)



- Time Interval (s)
- Electric Current (A)
- Thermodynamic Temperature (K)
- Luminous Intensity (cd)
- Amount of Substance (mol)

Traceability

The ability to relate a measurement result to a metrological reference through an unbroken chain of comparisons, all with known uncertainties.

Uncertainty of Measurement

Parameter, associated with the result of a measurement, which characterizes the dispersion of the values that could reasonably be attributed to the measurand.

2.0 Critical Process for Estimating Uncertainty of Measurement

There are essential actions that must be performed for a medical laboratory to successfully implement an Uncertainty of Measurement Program. These are found in the table below, and will be explained in the following sections.

Essential Actions	Output of Action
Categorize examinations	Document identifying examinations as Category 1, Category 2, Category 3, or Category 4. <ul style="list-style-type: none"> • Category 3 and Category 4 examinations will require UM identification. • Category 2 examinations will require evidence of compliance with the test method and compliance with required reporting instructions.
For each Category 3 or Category 4 examination, define the measurand of the method as well as clinically significant limitations and interferences.	Document identifying, for each Category 3 or Category 4 examination method, the measurand of the method along with any clinically significant limitations and interferences. <ul style="list-style-type: none"> • The identification of the clinically significant limitations and interferences must be from credible sources, and these sources should be known.
For each Category 3 or Category 4 examination, identify the components of UM.	Document identifying the UM components for each Category 3 or Category 4 examination.

	<ul style="list-style-type: none"> Generally, this may be the long term QC imprecision data. However, it may also include the published UM of calibrators.
For each Category 3 or Category 4 examination, record means long-term imprecision QC data to serve as the estimate of UM.	Document identifying the UM for each Category 3 or Category 4 examination.
Where applicable, determine Target Uncertainty for each examination.	The reliability needed for a reported measured value may differ for each clinical purpose. For example, for what purpose is this analysis conducted and what would be the targeted UM such that the clinician can confidently apply the significance of the value for patient care?
Where applicable, compare and contrast the examination UM to the Target Uncertainty.	Document a review of significant contributors to total analytical imprecision when the Target Uncertainty is not met, as well as the resolution.
For each UM determined, identify the numerical significance to reflect the UM of the method.	Document the determination of numerical significance.
Coordinate with clinicians the availability of UM information.	Documentation of clinician consideration of necessity of UM information. Appropriate identification of UM parameter on test reports should be identified where determined to be necessary.
Monitor UM estimates over time.	Documentation of on-going monitoring, such as the collection and analysis of QC data over time.


Attention will now be given to each of these actions in detail.

3.0 Implementation of Action Steps

This section will provide a closer look at each action step so that the user can more easily implement a UM program.

Categorize Examinations


A medical laboratory should begin with the identification of all examinations within the scope of accreditation. The following categories should then be applied to determine which examinations warrant Uncertainty of Measurement determination.

	<i>The American Association for Laboratory Accreditation</i>	
	P603e: Annex- Policy on Estimating Measurement Uncertainty for Medical Testing Laboratories	Document Issued: November 6, 2009
		Page 6 of 11

- 1) *Category 1: Methods that are reported on a qualitative basis, or on a categorical or nominal scale. In other words, there is an attribute answer to the examination inquiry. These methods are not kit driven. Here, UM is not meaningful because variation is due in large part to technical competency and not inherent in the measurement process itself.*
 - This category does not include methods that are reported on an ordinal scale, such as +, ++, +++, or +++++. It does include such an examination to determine the identification of a bacterial organism.

- 2) *Category 2: Well-recognized test methods that use kits or prepared reagents to determine qualitative results that are on an ordinal scale. Here the lab satisfies the need for uncertainty estimates by following the published method, meeting performance requirements (such as proficiency tests) and reporting in accordance with the published method.*
 - Category 2 tests are those qualitative tests where all of the components of the analysis (of the kit) fall under a package insert.
 - i. This package insert is approved by the FDA for human testing and version controlled by the manufacturer. Additionally, it contains uncertainty of measurement information appropriate for the test.
 - Examples of this system would be the Rapid Plasmin Reagin, and Red Cell Antibody Identification Panels.

- 3) *Category 3: Well-recognized quantitative and semi-quantitative methods that are governed by FDA approved test systems, including package inserts for reagents and instrument manuals for equipment.*
 - The laboratory must determine their uncertainty of measurement based on the reagent package insert performance criteria as well as the instrument performance criteria, and would typically use the internal quality control data to estimate uncertainty of measurement.
 - Some test results provide a qualitative result (positive or negative) based on quantitative responses. If the cut-off point is pre-determined, the possibility of having “indeterminate” responses exists to account for the UM in the establishment of the cut-off. The results closest to the cut-off are most at risk, and should be used as the basis in determining the UM of the examination method.
 - In these cases, UM may be expressed as any one or more of the following:
 - Traditional UM statement for samples at levels near the cut-off value.
 - A statement about false classification rates for results near the cut-off.
 - Overall rates of correctness for different known classes of samples (known positives, known negatives, sensitivity, specificity, etc.)

	<i>The American Association for Laboratory Accreditation</i>	
	P603e: Annex- Policy on Estimating Measurement Uncertainty for Medical Testing Laboratories	Document Issued: November 6, 2009
	Page 7 of 11	

4) *Category 4: In-house developed tests that generate quantitative data.*

- For these methods, UM must be estimated using available data, published information, and/or designed experiments.
 - Some test results provide a qualitative result (positive or negative) based on quantitative responses. If the cut-off point is pre-determined, the possibility of having “indeterminate” responses exists to account for the UM in the establishment of the cut-off. The results closest to the cut-off are most at risk, and should be used as the basis in determining the UM of the examination method.
 - In these cases, UM may be expressed as any one or more of the following:
 - Traditional UM statement for samples at levels near the cut-off value.
 - A statement about false classification rates for results near the cut-off.
 - Overall rates of correctness for different known classes of samples (known positives, known negatives, sensitivity, specificity, etc.)


There should be some sort of evidence that this classification process took place for all examinations within the scope of accreditation. The laboratory should then prepare to provide the UM for all examinations requiring UM estimates. The following steps apply only to those examinations requiring the UM estimate.

Define the Measurand for Each Examination Requiring UM Estimates

For each Category 3 and 4 examination, the medical laboratory must specify what is actually being measured by the test method. For example, many examinations have high analytical specificity and thus measure only the substance they are designed to measure. However, some examinations are not as specific and thus tend toward cross reactivity and interfering substances which will be included in the final value. So, for each Category 3 and 4 examination, documentation must exist that identifies:

- The analytical method used.
- The substance the method is designed to measure.
- What is actually measured (the measurand).
- Any diagnostic limitations to the method.
- Any cross-reacting and interfering substances that impact the clinical interpretation of the values.
 - These should be known from credible and identifiable sources.

For example, when measuring for enzymatic activity, the examination does not necessarily directly measure the level of the enzyme, but rather the activity of the enzyme. So, in examinations for Alkaline Phosphatase, Alkaline Phosphatase activity is what is actually measured, not the Alk Phos level itself. Thus, Alk Phos is the analyte, and Alk Phos activity is the measurand.

	<i>The American Association for Laboratory Accreditation</i>	
	P603e: Annex- Policy on Estimating Measurement Uncertainty for Medical Testing Laboratories	Document Issued: November 6, 2009
		Page 8 of 11

Identify the Components of UM

As noted earlier, there are two sources of uncertainty in quantitative clinical laboratory testing that may exist. These include:


- 1) The normal variation or imprecision associated with running the method repetitively. So, if a known substance is assayed, its value may be, over time: 100, 105, 110, 102, 106, 108, 109, 107, 105, and 103. The standard deviation of these values can be termed the imprecision of the examination method. (Note: In no way does this example imply that 10 values should be used to calculate standard deviation; it is for illustrative purposes only).
 - This can be termed “common cause variation” because it is predictable in nature and inherent to the process. It cannot be eliminated, only reduced.
 - i. If the variation is not common cause, that is, it is not predictable in pattern, the process must be evaluated to bring it into a state of common cause variation (statistical control) before an imprecision measure can be made. In this case, assignable cause variation is present and must be eliminated.
- 2) The uncertainty associated with the calibrator used in the examination method.
 - This UM should be provided by the commercial supplier.
 - If the calibrator is not obtained from a commercial supplier, a UM estimate must be determined.

When both sources of variation exist, the UM of the examination system may consist of a total of these sources. The key is to determine what the contribution of the components is and then decide what contribution is significant. In many cases, the calibrator will most likely result in a negligible contribution.

Record Mean Long-Term Imprecision QC Data as UM Estimate

For medical laboratory examinations, imprecision estimates such as standard deviation (SD) and coefficient of variation (CV) provide the UM estimate required, if the QC process includes all the steps and components involved in examining patient samples. These data are best collected over time across as many routine-operating conditions as possible to provide the most reliable estimate of UM. The SD or the CV represents the Quality Control data associated with the examination procedures.

- For established methods collect at least 6 months worth of internal QC data to calculate SD or CV
- 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 UM. Continue to evaluate until the long term can be established.

	<i>The American Association for Laboratory Accreditation</i>	
	P603e: Annex- Policy on Estimating Measurement Uncertainty for Medical Testing Laboratories	Document Issued: November 6, 2009
		Page 9 of 11

- For UM purposes UM represents the 95% confidence interval.
 - ± 2.0 SD
- In general, the more data collected, the more reliable the estimate.

Establish the Target Uncertainty, Where Applicable; Compare UM to Goal

From ISO/PDTS 25680.7: The value of the measurand coupled with the calculated UM should be compared to either a biological reference value or a clinical decision limit. Neither of these should have a UM (ISO/PDTS 25680.7). The calculated UM 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.

Determine the Numerical Significance of UM Estimates and Clinical Results


The significant numbers used represent not only the value of a result, but also the certainty with which the result was determined. The key is to evaluate the imprecision data. Generally, the larger the imprecision value (SD or CV) the fewer significant digits that should be used. In other words, with great variation, 110 can look a lot like 107. But, with very little variation, 110 can be very different from 110.5. The laboratory must establish, based on its variation data, what represents a meaningful difference in values.

Interface with Clinicians on the Appropriate Use of UM Estimates

In many cases, UM estimates can contribute to patient care. Thus, in consult with clinicians, the laboratory must determine these results that could significantly impact clinical interpretation and subsequent patient management. It should also consider if it is necessary to include UM estimates in actual patient reports. As a result, it is expected that procedures exist in the laboratory for informing clinicians of significant UM information in a way that will be meaningful for clinical use. The expression of the UM concept is at the discretion of the laboratory such as a confidence expression. Now that there is an understanding of the activities necessary to establish UM estimates, attention will now turn to the monitoring of the UM.


4.0 Monitoring

As with any estimate, changes can occur with time. As more data are collected over time, the more stable the estimate becomes. Thus, for each examination with an UM estimate, an on-going monitoring program must be in place.

	<i>The American Association for Laboratory Accreditation</i>	
	P603e: Annex- Policy on Estimating Measurement Uncertainty for Medical Testing Laboratories	Document Issued: November 6, 2009
		Page 10 of 11

Components of a Monitoring Program

- Sampling Plan
 - The laboratory must determine when, where, and how QC data will be collected. Generally, all QC and PT data should be used to evaluate the established estimate of UM. The UM would then be adjusted based on these data.
 - These data are best collected over time across as many routine-operating conditions as possible to provide the most reliable estimate of UM.
 - The laboratory must determine how many measurements will be part of the sample. For example, perhaps the \bar{x} (mean) will be comprised of a certain amount of measurements, like 5 measures of one level of QC. Or perhaps each measurement will be tracked. Based on this sampling plan, the appropriate type of statistical chart can be used for monitoring, for example, an \bar{x} -R (average and range chart) or an xmR (individual measures and moving range chart).
- Rules of Monitoring
 - The laboratory must apply statistical rules to ensure that the examinations monitored are in a state of statistical control (exhibiting only common cause variation).
 - When a process is exhibiting more than common cause variation, measures of imprecision, such as standard deviation and coefficient of variation are meaningless.
 - Unacceptable results in proficiency tests should lead to a review of UM, unless a special cause source of variation is identified
- Actions to maintain currency of UM
 - The laboratory must define actions it will take when examinations with UM concern 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 UM estimate will be communicated.
 - This action should also include how the new UM estimate will be re-established, documented, and communicated after statistical control is again achieved.
 - The 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.

	<i>The American Association for Laboratory Accreditation</i>	
	P603e: Annex- Policy on Estimating Measurement Uncertainty for Medical Testing Laboratories	Document Issued: November 6, 2009
		Page 11 of 11

In conclusion, the laboratory has the responsibility to establish UM estimates for applicable examinations with regard to fitness for clinical use. As part of that establishment, the laboratory must implement a monitoring plan to ensure the integrity of it's UM estimates.

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