

Archived Document

This archived document is no longer being reviewed through the CLSI Consensus Document Development Process. However, this document is technically valid as of June 2018. Because of its value to the laboratory community, it is being retained in CLSI's library.



January 2012

EP29-A

Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline

This guideline describes a practical approach to assist clinical laboratories in developing and calculating useful estimates of measurement uncertainty, and illustrates their application in maintaining and improving the quality of measured values used in patient care.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

Clinical and Laboratory Standards Institute

Setting the standard for quality in medical laboratory testing around the world.

The Clinical and Laboratory Standards Institute (CLSI) is a not-for-profit membership organization that brings together the varied perspectives and expertise of the worldwide laboratory community for the advancement of a common cause: to foster excellence in laboratory medicine by developing and implementing medical laboratory standards and guidelines that help laboratories fulfill their responsibilities with efficiency, effectiveness, and global applicability.

Consensus Process

Consensus—the substantial agreement by materially affected, competent, and interested parties—is core to the development of all CLSI documents. It does not always connote unanimous agreement, but does mean that the participants in the development of a consensus document have considered and resolved all relevant objections and accept the resulting agreement.

Commenting on Documents

CLSI documents undergo periodic evaluation and modification to keep pace with advancements in technologies, procedures, methods, and protocols affecting the laboratory or health care.

CLSI's consensus process depends on experts who volunteer to serve as contributing authors and/or as participants in the reviewing and commenting process. At the end of each comment period, the committee that developed the document is obligated to review all comments, respond in writing to all substantive comments, and revise the draft document as appropriate.

Comments on published CLSI documents are equally essential, and may be submitted by anyone, at any time, on any document. All comments are managed according to the consensus process by a committee of experts.

Appeals Process

When it is believed that an objection has not been adequately considered and responded to, the process for appeals, documented in the CLSI Standards Development Policies and Processes, is followed.

All comments and responses submitted on draft and published documents are retained on file at CLSI and are available upon request.

Get Involved—Volunteer!

Do you use CLSI documents in your workplace? Do you see room for improvement? Would you like to get involved in the revision process? Or maybe you see a need to develop a new document for an emerging technology? CLSI wants to hear from you. We are always looking for volunteers. By donating your time and talents to improve the standards that affect your own work, you will play an active role in improving public health across the globe.

For additional information on committee participation or to submit comments, contact CLSI.

Clinical and Laboratory Standards Institute
950 West Valley Road, Suite 2500
Wayne, PA 19087 USA
P: +1.610.688.0100
F: +1.610.688.0700
www.clsi.org
standard@cls.org

ISBN 1-56238-787-1 (Print)
ISBN 1-56238-788-X (Electronic)
ISSN 1558-6502 (Print)
ISSN 2162-2914 (Electronic)

EP29-A
Vol. 32 No. 4
Formerly C51-A
Vol. 32 No. 4

Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline

Volume 32 Number 4

Anders Kallner, MD, PhD
James C. Boyd, MD
David L. Duewer, PhD
Claude Giroud, PhD
Aristides T. Hatjimihail, MD, PhD
George G. Klee, MD, PhD

Stanley F. Lo, PhD, DABCC, FACB
Gene Pennello, PhD
David Sogin, PhD
Daniel W. Tholen, MS
Blaza Toman, PhD
Graham H. White, PhD

Abstract

Clinical and Laboratory Standards Institute document EP29-A—*Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline* describes the principles of estimating measurement uncertainty and provides guidance to clinical laboratories and *in vitro* diagnostic device manufacturers on the specific issues to be considered for implementation of the concept in laboratory medicine. This document illustrates the assessment of measurement uncertainty with both bottom-up and top-down approaches. The bottom-up approach suggests that all possible sources of uncertainty are identified and quantified in an uncertainty budget. A combined uncertainty is calculated using statistical propagation rules. The top-down approach directly estimates the measurement uncertainty results produced by a measuring system. Methods to estimate the imprecision and bias are presented theoretically and in worked examples.

Clinical and Laboratory Standards Institute (CLSI). *Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline*. CLSI document EP29-A (ISBN 1-56238-787-1 [Print]; ISBN 1-56238-788-X [Electronic]). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2012.

The Clinical and Laboratory Standards Institute consensus process, which is the mechanism for moving a document through two or more levels of review by the health care community, is an ongoing process. Users should expect revised editions of any given document. Because rapid changes in technology may affect the procedures, methods, and protocols in a standard or guideline, users should replace outdated editions with the current editions of CLSI documents. Current editions are listed in the CLSI catalog and posted on our website at www.clsi.org. If your organization is not a member and would like to become one, and to request a copy of the catalog, contact us at: Telephone: 610.688.0100; Fax: 610.688.0700; E-Mail: customerservice@cls.org; Website: www.clsi.org.



Copyright ©2012 Clinical and Laboratory Standards Institute. Except as stated below, any reproduction of content from a CLSI copyrighted standard, guideline, companion product, or other material requires express written consent from CLSI. All rights reserved. Interested parties may send permission requests to permissions@clsi.org.

CLSI hereby grants permission to each individual member or purchaser to make a single reproduction of this publication for use in its laboratory procedure manual at a single site. To request permission to use this publication in any other manner, e-mail permissions@clsi.org.

Suggested Citation

CLSI. *Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline*. CLSI document EP29-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.

Previous Edition:

December 2010

Archived:

June 2018

ISBN 1-56238-787-1 (Print)
ISBN 1-56238-788-X (Electronic)
ISSN 1558-6502 (Print)
ISSN 2162-2914 (Electronic)

Committee Membership

Consensus Committee on Clinical Chemistry and Toxicology

David G. Grenache, PhD,
DABCC, FACB
Chairholder
University of Utah, ARUP
Laboratories
Salt Lake City, Utah, USA

Loralie J. Langman, PhD
Vice-Chairholder
Mayo Clinic
Rochester, Minnesota, USA

Julianne Cook Botelho, PhD
Centers for Disease Control and
Prevention
Atlanta, Georgia, USA

Yung W. Chan, MT(ASCP)
FDA Center for Devices and
Radiological Health
Rockville, Maryland, USA

Corinne R. Fantz, PhD, DABCC
Emory University
Atlanta, Georgia, USA

T. Scott Isbell, PhD, DABCC,
FACB
Nova Biomedical Corporation
Chicago, Illinois, USA

Jessie Shih, PhD
Abbott
Abbott Park, Illinois, USA

Graham H. White, PhD
Flinders Medical Centre
Bedford Park, South Australia

Jack Zakowski, PhD, FACB
Beckman Coulter
Brea, California, USA

Document Development Committee on Expression of Measurement Uncertainty in Laboratory Medicine

Anders Kallner, MD, PhD
Chairholder
Karolinska Hospital
Stockholm, Sweden

James C. Boyd, MD
UVA Health System
Charlottesville, Virginia, USA

David L. Duewer, PhD
National Institute of Standards and
Technology
Gaithersburg, Maryland, USA

Claude Giroud, PhD
Bio-Rad Laboratories, Inc.
Marnes-la-Coquette, France

Stanley F. Lo, PhD, DABCC,
FACB
Children's Hospital of Wisconsin
Milwaukee, Wisconsin, USA

Gene Pennello, PhD
FDA Center for Devices and
Radiological Health
Silver Spring, Maryland, USA

Daniel W. Tholen, MS
American Association for
Laboratory Accreditation
Traverse City, Michigan, USA

Graham H. White, PhD
Flinders Medical Centre
South Australia, Australia

Staff

Clinical and Laboratory Standards
Institute
Wayne, Pennsylvania, USA

Luann Ochs, MS
*Vice President, Standards
Development*

Ron S. Quicho
Staff Liaison

Patrice Polgar, BA
Project Manager

Megan P. Larrisey, MA
Editor

Ryan J. Torres, BA
Assistant Editor

Acknowledgments

This guideline was prepared by the Clinical and Laboratory Standards Institute (CLSI) as part of a cooperative effort with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) to work toward the advancement and dissemination of laboratory standards on a worldwide basis. CLSI gratefully acknowledges the participation of IFCC expert Graham H. White, PhD, on this project.

CLSI, the Consensus Committee on Clinical Chemistry and Toxicology, and the Document Development Committee on Expression of Measurement Uncertainty in Laboratory Medicine gratefully acknowledge the following individuals for important contributions made during the development of this document:

Aristides Hatjimihail, MD, PhD
Hellenic Complex Systems Laboratory
Drama, Greece

George G. Klee, MD, PhD
Mayo Clinic
Rochester, Minnesota, USA

David Sogin, PhD
Highland Park, Illinois, USA

Blaza Toman, PhD
National Institute of Standards and Technology
Gaithersburg, Maryland, USA

Acknowledgment in Memoriam of Richard R. Miller, Jr.

CLSI, the Consensus Committee on Clinical Chemistry and Toxicology, and the Document Development Committee on Expression of Measurement Uncertainty in Laboratory Medicine also wish to recognize the contributions of Richard R. Miller, Jr., champion of measurement excellence within the clinical laboratory communities. Rick was instrumental in the development of this document and served as subcommittee chairholder until his untimely passing in July 2007. Rick's clear vision, deep wisdom, gentle wit, and above all his spirit of collegiality guided the document's evolution and inspired the document development committee's efforts to bring it to fruition.

Contents

Abstract.....	i
Committee Membership.....	iii
Foreword.....	vii
1 Scope.....	1
2 Introduction.....	1
3 Terminology.....	2
3.1 A Note on Terminology	2
3.2 Metrological Concepts and Terms as Applied in Laboratory Medicine	3
3.3 Definitions of Concepts and Terms Used in This Document	4
3.4 Abbreviations and Acronyms	11
3.5 Symbols	12
3.6 Summary Statistics	12
4 Strategies to Estimate Measurement Uncertainty	17
4.1 Potential Sources of Measurement Uncertainty.....	18
4.2 Use of Readily Available Data	18
4.3 Combining Random and Systematic Measurement Errors: Two Approaches.....	19
5 Overview of Measurement Uncertainty	21
5.1 Introduction to Terminology of Measurement Uncertainty	21
6 Bottom-up Uncertainty Estimation.....	22
6.1 Sources of Uncertainty.....	22
6.2 Uncertainty Budget.....	24
6.3 Quantification of Uncertainties.....	24
6.4 Measurement Function and Estimation of the Combined Standard Uncertainty.....	25
6.5 Combining Measurement Uncertainty With Uncertainties From Other Sources	28
7 Top-Down Approach to Estimation of Measurement Uncertainty	28
7.1 General.....	28
7.2 Assessment of Measurement Uncertainty Using Internal Quality Control Data	29
7.3 Analysis of Variance—Variance Components	29
7.4 Uncertainty Profiles	31
7.5 Use of Results From Interlaboratory Comparisons.....	32
7.6 Unsatisfactory Results	33
8 Bias Assessment	33
8.1 Bias	33
8.2 Bias Correction	33
8.3 Estimating the Uncertainty of the Bias Correction	34
9 Uses of Uncertainty Estimates	37
9.1 Reporting Measurement Results and Their Uncertainties	37
9.2 Number of Significant Digits.....	38
9.3 Clinical Use of Measurement Uncertainty Estimates	38
10 Summary	44
References.....	46

Contents (Continued)

Additional References.....	49
Appendix A. Transformation of Type B Limit Specifications	50
Appendix B. Uncertainty Estimates From Routine Quality Control Results.....	53
The Quality Management System Approach	56
Related CLSI Reference Materials	57

Foreword

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. Quantification of the variability of measurement results also allows a result to be meaningfully compared with the results of other similar measurements that may have been made at different times using the same measurement system. The concept of measurement uncertainty provides a theoretical and practical framework for objectively estimating the reliability of results produced by any given measurement system.

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. Uncertainty estimates at various analyte concentrations also contribute to determining uncertainty profiles, which can be important in defining the measuring interval of measurement systems to ensure that the quality of results issued meets clinical requirements.

This document describes the principles of estimating measurement uncertainty and gives guidance on the specific issues to be considered for implementation of the concept in laboratory medicine. The concept of measurement uncertainty and its use in measuring quantities in laboratory medicine is provided for clinical laboratories and *in vitro* diagnostic device manufacturers.

Key Words

Bias, bottom-up, measurement uncertainty, precision, top-down, trueness

Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline

1 Scope

This guideline explains the concept, estimation, and application of measurement uncertainty in the field of clinical laboratory medicine. The recommendations provided are consistent with the *Guide to the expression of uncertainty in measurement* (GUM)¹ and with the International Organization for Standardization (ISO) standards concerned with laboratory accreditation.^{2,3}

This guideline briefly discusses, but does not fully address, the following nonmeasurement sources of uncertainty of a measurement result:

- Biological variation of the measurand
- Pre- and postmeasurement processes

The guideline discusses the definition of what is intended to be measured, lists sources of measurement uncertainty, describes the generation of statistical estimates of uncertainties and their combination, and discusses the use of uncertainty estimates. The guideline applies only to quantitative measurements. In measurement procedures that are reported in qualitative terms based on a quantitative measurement, the uncertainty at the threshold(s) for a qualitative interpretation should be considered when making the qualitative assessment.

This guideline is intended for clinical laboratories and *in vitro* diagnostic (IVD) device manufacturers.

2 Introduction

Regardless of method, repeated measurements produce different results due to inherent variations within a sufficiently sensitive measurement procedure. Some knowledge of the result variability expected from a given measurement system is required if results are to be meaningfully compared with previous results from the same patient or important clinical decision limits. In addition, evaluation and elimination of bias in a measuring system relative to the relevant reference material or reference procedure is essential if results from different laboratories using the same or different measuring systems are to be compared for the same patient.

Characterization of the variability of repeated measurement results and identification of the factors that contributed to that variability can provide useful insights into the reliability of results and potential means for improvement. Existing quality control (QC) and method verification data can be used to define the performance characteristics of routine measuring systems. This document provides guidance on how measurement uncertainty can be estimated and used in the field of laboratory medicine. The principles for expression of measurement uncertainty provided in this document illustrate how the components of measurement uncertainty can be combined to help estimate the performance characteristics that can be reliably achieved by the measuring system.

The objectives of this document are to:

- Familiarize the reader with the concept of measurement uncertainty.
- Describe the processes of implementing the concept of measurement uncertainty in laboratory medicine.

- Describe practical approaches to developing relevant and useful estimates of measurement uncertainty.
- Discuss uses of the measurement uncertainty information obtained.

3 Terminology

3.1 A Note on Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization wherever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. CLSI recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in CLSI, ISO, and European Committee for Standardization (CEN) documents; and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. In light of this, CLSI's consensus process for development and revision of standards and guidelines focuses on harmonization of terms to facilitate the global application of standards and guidelines.

A hierarchy of terminology was agreed upon, involving ISO (www.iso.org), CEN (www.cen.eu), CLSI (www.clsi.org), and the Bureau International des Poids et Mesures (BIPM) (www.bipm.org).

Essentially, new documents are obliged to adhere to the *International Vocabulary of Metrology – Basic and General Concepts and Associated Terms* (VIM),⁴ whenever an ambiguity in the interpretation or understanding of terms occurs. The VIM deals with general metrology and terminology that should be useful for most disciplines that measure quantities.

The understanding of a few terms has changed during the last decade as the concepts have developed. Particularly, *trueness* (measurement trueness) is defined as expressing the closeness of agreement between the average of an infinite number of replicate measurements and a reference value; and *precision* (measurement precision) is defined as closeness of agreement between indications or measured quantity values obtained by repeated measurements of the same sample and quantity under specified conditions. Consequently, *accuracy* (measurement accuracy) is the closeness of agreement between a measured value and a true quantity value of a measurand. Thus, this concept comprises both trueness and precision, and applies to a single result. *Measuring interval* has replaced *reportable range* when referring to “a set of values of a measurand for which the error of a measuring instrument (test) is intended to lie within specified limits.” An *interval* $[a;b]$ is delineated by two limits a and b ($b > a$), whereas a *range* ($r[a;b]$) is expressed as the difference between b and a ($b - a$). Thus, the range of the interval $[a;b]$ is the difference ($b - a$) that is denoted by $r[a;b]$.

The term *measurand* is used when referring to the quantity intended to be measured instead of *analyte* (component represented in the name of a measurable quantity); the term *measurement procedure* replaces *analytical method* for a set of operations, used in the performance of particular measurements according to a given method.

Verification focuses on whether specifications of a measurement procedure can be achieved, whereas *validation* verifies that the procedure is fit for purpose. Both concepts can describe procedures of varying complexity. This document specifically deals with verification.

In this document, the terms *preanalytical*, *analytical*, and *postanalytical* appear parenthetically after the terms *preexamination*, *examination*, and *postexamination* where appropriate. Furthermore, in order to align the usage of terminology in this document with that of ISO and CLSI document GP02,⁵ the term *standard operating procedure (SOP)* has been replaced with the term *procedures/instructions*.

3.2 Metrological Concepts and Terms as Applied in Laboratory Medicine

Metrology, the science of measurement, has developed concepts and definitions (see Section 3.3) to describe the theoretical and practical aspects of measurements. The application of some commonly used metrological terms in laboratory medicine is illustrated here.

When considering some properties of erythrocytes, for example, one notes that one property is the color red, another is the biconcave disc shape, another is the diameter, and another is the volume. Some of these properties are measurable (ie, have a magnitude that can be expressed as a number and a unit), and some are not (eg, the nominal property of color). In metrology, a measurable property is termed a **quantity**. To adequately define a given quantity, it is necessary to also identify the **system** in which it is located (eg, blood, urine, expired air), the **component** of interest (eg, erythrocyte), and the **kind of quantity** (eg, length, light absorption).

For example, if the laboratory has a routine measuring system for estimating red blood cell diameters, the system is venous blood, the quantity is diameter, and the kind of quantity is length. Together, these terms describe the quantity the laboratory intends to measure, the term for which is **measurand**. In this example, it happens that the measurand is directly measurable by the measuring system. However, with clinical laboratory methods, it is rarely possible to directly measure the measurand (quantity intended to be measured), eg, creatinine molecules in serum cannot be directly counted. Therefore, such methods must indirectly measure the measurand via another quantity that can be quantitatively related to the measurand, eg, by use of a calibration function.

In the case of measuring creatinine concentration in serum, the measurand (quantity intended to be measured) is the amount-of-substance concentration (kind of quantity) of creatinine (component) in serum (system). However, because the creatinine concentration cannot be directly measured, the absorbance of a colored reaction product between creatinine and alkaline picrate is measured. In this case, the color is the component, the absorbance at a given wavelength is the kind of quantity, and the system is serum. The magnitude of the absorbance detected by the measuring system is termed the **indication**. The indication is then related to the creatinine concentration by a calibration function, using a reference material with a known creatinine concentration. Thus, it is usually the case for clinical laboratory measurement methods that the quantity actually measured and the measurand differ; ideally, through the calibration procedure, the numerical value is the same. If the serum concentration of creatinine were measured by an enzymatic procedure, then the quantity would be different but the measurand and its kind of quantity would be unchanged. In this particular case, the quantity value may differ owing to the difference in chemical **selectivity** of the measurement procedures.

In summary, a minimal description of a measurand using the International Federation of Clinical Chemistry and Laboratory Medicine/International Union of Pure and Applied Chemistry (IFCC/IUPAC) nomenclature is “S-Creatinine; amount-of-substance concentration = NN $\mu\text{mol/L}$ ” or “S-Creatinine; mass concentration = NM mg/L .” The measurement result is expressed as a number times a unit, and the unit must correspond to the kind of quantity, eg, $\mu\text{mol/L}$ and mg/L , respectively, in this example. **NOTE:** To avoid confusion between the separator “-” and mathematical notation for subtraction “-”, the example calculations in this document represent generic values for such measurands as {*measurand*}; eg, the value of the measurand S-Creatinine concentration is represented {S-Creatinine}. The kind of quantity is given only if the meaning is ambiguous.

In laboratory medicine, measurands are sometimes not unequivocally defined, eg, a protein subject to glycation leading to complex and variable mixtures in a system such as human chorionic gonadotropin species in serum is a “multimeasurand.” This may lead to varying interactions with the measuring system and is termed **definitional uncertainty**. However, when the quantity actually measured depends on the **measuring system** (eg, a specific antibody and/or epitope), the description of the quantity would need to include relevant details of the measuring system (eg, molecular species, measurement system details, and

calibrator). In the case of proteins and other complex materials, the metrological traceability may only be possible to a defined measurement procedure.

3.3 Definitions of Concepts and Terms Used in This Document

certified reference material (CRM) – reference material, accompanied by documentation issued by an authoritative body and providing one or more specified property values with associated uncertainties and traceabilities, using valid procedures; **EXAMPLE:** Human serum with assigned quantity value for the concentration of cholesterol and associated measurement uncertainty stated in an accompanying certificate, used as a calibrator or measurement trueness control material; **NOTE 1:** “Documentation” is given in the form of a “certificate” (see ISO Guide 31:2000⁶); **NOTE 2:** Procedures for the production and certification of CRMs are given, eg, in ISO Guide 34⁷ and ISO Guide 35⁸; **NOTE 3:** In this definition, “uncertainty” covers both “measurement uncertainty” and “uncertainty associated with the value of a nominal property,” such as for identity and sequence. “Traceability” covers both “metrological traceability of a quantity value” and “traceability of a nominal property value” (JCGM 200:2008)⁴; **NOTE 4:** Specified quantity values of CRMs require metrological traceability with associated measurement uncertainty.

coefficient of variation (CV) – for a non-negative characteristic, the ratio of the standard deviation to the average (ISO 3534-1)⁹; **NOTE 1:** The term “relative standard deviation” is sometimes used as an alternative to “coefficient of variation” but this use is not recommended; **NOTE 2:** It is a measure of relative imprecision; it is often multiplied by 100 and expressed as a percentage and abbreviated as %CV.

combined standard measurement uncertainty//combined standard uncertainty – standard measurement uncertainty that is obtained using the individual standard measurement uncertainties associated with the input quantities in a measurement model (JCGM 200:2008 § 2.31)⁴; **NOTE:** The symbol for a combined standard uncertainty is u_c (JCGM 100:2008 § 3.3.6).¹

commutability – (of a reference material) property of a reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two given measurement procedures, and the relation obtained among the measurement results for other specified materials (JCGM 200:2008)⁴; **NOTE:** The reference material in question is usually a reference material (calibrator) and the other specified materials are usually routine samples (modified from JCGM 200:2008 § 5.15).⁴

conventional quantity value//conventional value of a quantity//conventional value – quantity value attributed by agreement to a quantity for a given purpose; **EXAMPLE:** Conventional quantity value of a given mass standard, $m = 100.00347$ g; **NOTE 1:** The term “conventional true quantity value” is sometimes used for this concept, but its use is discouraged; **NOTE 2:** Sometimes a conventional quantity value is an estimate of a true quantity value; **NOTE 3:** A conventional quantity value is generally accepted as being associated with a suitably small measurement uncertainty, which might be zero (JCGM 200:2008 § 2.12).⁴

covariance – the covariance of two random variables is a measure of their mutual dependence (JCGM 100:2008 § C3.4)¹; **NOTE:** The covariance between two random variables x and y can be symbolized s_{xy} or $\text{cov}(x,y)$.

coverage factor – number larger than one by which a combined standard measurement uncertainty is multiplied to obtain an expanded measurement uncertainty (JCGM 200:2008 § 2.38)⁴; **NOTE:** A coverage factor is usually symbolized k (JCGM 200:2008).⁴

coverage interval – interval containing the set of true quantity values of a measurand with a stated probability, based on the information available; **NOTE 1:** A coverage interval does not need to be

centered on the chosen measured quantity value; **NOTE 2:** A coverage interval should not be termed “confidence interval,” to avoid confusion with the statistical concept; **NOTE 3:** A coverage interval can be derived from an expanded measurement uncertainty (JCGM 200:2008 § 2.36).⁴

coverage probability – probability that the set of true quantity values of a measurand is contained within a specified coverage interval; **NOTE 1:** This definition pertains to the Uncertainty Approach as presented in the GUM¹; **NOTE 2:** The coverage probability is also termed “level of confidence” in the GUM¹ (JCGM 200:2008 § 2.37).⁴

definitional uncertainty – component of **measurement uncertainty** resulting from the finite amount of detail in the definition of a **measurand**; **NOTE 1:** Definitional uncertainty is the practical minimum measurement uncertainty achievable in any measurement of a given measurand; **NOTE 2:** Any change in the descriptive detail leads to another definitional uncertainty (JCGM 200:2008 § 2.27).⁴

expanded measurement uncertainty//expanded uncertainty – product of a combined standard measurement uncertainty and a factor larger than the number one; **NOTE 1:** The factor depends upon the type of probability distribution of the output quantity in a measurement model and on the selected coverage probability (JCGM 200:2008 § 2.35)⁴; **NOTE 2:** An expanded uncertainty is symbolized *U*.

indication – quantity value provided by a measuring instrument or a measuring system; **NOTE 1:** An indication is a signal or reading from a measuring system. An indication is often given by the position of a pointer on the display for analog outputs, a displayed or printed number for digital outputs, a code pattern for code outputs, or an assigned quantity value for material measures; **NOTE 2:** An indication and a corresponding value of the quantity being measured are not necessarily values of quantities of the same kind (JCGM 200:2008 § 4.1).⁴

input quantity in a measurement model//input quantity – quantity that must be measured, or a quantity, the value of which can be otherwise obtained, in order to calculate a measured quantity value of a measurand; **NOTE:** An input quantity in a measurement model is often an output quantity of a measuring system; **EXAMPLE:** The temperature, cofactor concentrations, duration of incubation, and change in absorbance due to the change in product concentration can be input quantities in a measurement model for catalytic concentration of an enzyme in blood plasma (JCGM 200:2008 § 2.50).⁴

internal quality control (IQC) – set of procedures undertaken by laboratory staff for the continuous monitoring of operation and the results of measurements in order to decide whether results are reliable enough to be released.¹⁰

measurand – quantity intended to be measured; **NOTE 1:** The specification of a measurand requires knowledge of the kind of quantity; description of the state of the phenomenon, body, or substance carrying the quantity, including any relevant component; and the chemical entities involved; **NOTE 2:** The measurement, including the measuring system and the conditions under which the measurement is carried out, might change the phenomenon, body, or substance such that the quantity being measured may differ from the measurand as defined. In this case, adequate correction is necessary; **NOTE 3:** In chemistry, “analyte,” or the name of a substance or compound, is sometimes used for “measurand.” This usage is erroneous because these terms do not refer to quantities, but only to a component of the measurand (modified from JCGM 200:2008 § 2.3)⁴; **EXAMPLE 1:** The “mass of protein in 24-hour urine from a given person at a given time” is a measurand. The component “protein” is sometimes termed “analyte”; **EXAMPLE 2:** The “amount-of-substance of glucose in plasma of a given person at a given time” is a measurand with the component “glucose”; **EXAMPLE 3:** The colloquial term “calcium” usually refers to either of the measurands’ “amount-of-substance concentration of total calcium in serum of a given person at a given time” or “amount-of-substance concentration of ionized calcium in serum of a given person at a given time.” In the first case, total calcium includes all fractions, which comprise free calcium ions (ionized calcium) and bound calcium (complex bound calcium and protein bound calcium).

measured quantity value//measured value of a quantity//measured value – quantity value representing a measurement result; **NOTE:** For a measurement involving replicate indications, each indication can be used to provide a corresponding measured quantity value. This set of individual measured quantity values can be used to calculate a resulting measured quantity value, such as an average or median, usually with a decreased associated measurement uncertainty (JCGM 200:2008 § 2.10).⁴

measurement – process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity; **NOTE 1:** Measurement does not apply to nominal properties; **NOTE 2:** Measurement presupposes a description of the quantity commensurate with the intended use of a measurement result, a measurement procedure, and a calibrated measuring system operating according to the specified measurement procedure, including the measurement conditions (JCGM 200:2008 § 2.1).⁴

measurement accuracy//accuracy of measurement//accuracy – closeness of agreement between a measured quantity value and a true quantity value of a measurand; **NOTE 1:** The concept “measurement accuracy” is not a quantity and is not given a numerical quantity value. A measurement is said to be more accurate when it offers a smaller measurement error; **NOTE 2:** The term “measurement accuracy” should not be used for “measurement trueness,” and the term “measurement precision” should not be used for “measurement accuracy,” which, however, is related to both these concepts (JCGM 200:2008 § 2.13)⁴; **NOTE 3:** “Measurement accuracy” is inversely related to “measurement error” and “measurement uncertainty,” and directly related to “measurement precision.”

measurement bias//bias – estimate of a systematic measurement error (JCGM 200:2008 § 2.18).⁴

measurement error//error of measurement//error – measured quantity value minus a reference quantity value; **NOTE 1:** The concept of “measurement error” can be used both: a) when there is a single reference quantity value to refer to, which occurs if a calibration is made by means of a measurement standard with a measured quantity value having a negligible measurement uncertainty or if a conventional quantity value is given, in which case the measurement error is known; and b) if the measurand is supposed to be represented by a unique true quantity value or a set of true quantity values of negligible interval, in which case the measurement error is not known (modified from JCGM 200:2008⁴); **NOTE 2:** The sign of the difference must be noted; **NOTE 3:** Generally, a known measurement error should be corrected using the best estimate of that measurement error. The measurement uncertainty of a correction is part of the combined measurement uncertainty (JCGM 200:2008 § 2.16).⁴

measurement function – function of quantities, the value of which, when calculated using known quantity values for the input quantities in a measurement model, is a measured quantity value of the output quantity in the measurement model; **NOTE 1:** If a measurement model $h(Y, X_1, \dots, X_n) = 0$ can explicitly be written as $Y = f(X_1, \dots, X_n)$, where Y is the output quantity in the measurement model, the function f is the measurement function. More generally, f may symbolize an algorithm, yielding for input quantity values $x_1, \dots, x_n$ a corresponding unique output quantity value $y = f(x_1, \dots, x_n)$; **NOTE 2:** A measurement function is also used to calculate the measurement uncertainty associated with the measured quantity value of Y (JCGM 200:2008 § 2.49).⁴

measurement model//model of measurement//model – mathematical relation among all quantities known to be involved in a measurement; **NOTE 1:** A general form of a measurement model is the equation $h(Y, X_1, \dots, X_n) = 0$, where Y , the output quantity in the measurement model, is the measurand, the quantity value of which is to be inferred from information about input quantities in the measurement model $X_1, \dots, X_n$; **NOTE 2:** In more complex cases in which there are two or more output quantities in a measurement model, the measurement model consists of more than one equation (JCGM 200:2008 § 2.48).⁴

measurement precision//precision – closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions;

NOTE 1: Measurement precision is usually expressed numerically by measures of imprecision, such as standard deviation, variance, or coefficient of variation under the specified conditions of measurement; **NOTE 2:** The “specified conditions” can range from repeatability to reproducibility conditions of measurement (see ISO 5725-3).¹¹

measurement procedure – detailed description of a measurement according to one or more measurement principles and to a given measurement method, based on a measurement model and including any calculation to obtain a measurement result; **NOTE:** A measurement procedure is usually documented in sufficient detail to enable an operator to perform a measurement.

measurement result/result of measurement – set of quantity values being attributed to a measurand together with any other available relevant information; **NOTE 1:** A measurement result generally contains “relevant information” about the set of quantity values, such that some may be more representative of the measurand than others. This may be expressed in the form of a probability density function; **NOTE 2:** A measurement result is generally expressed as a single measured quantity value and a measurement uncertainty. If the measurement uncertainty is considered to be negligible for some purpose, the measurement result may be expressed as a single measured quantity value. In many fields, this is the common way of expressing a measurement result; **NOTE 3:** In the traditional literature and in the previous edition of the VIM, measurement result was defined as a value attributed to a measurand and explained to mean an indication, or an uncorrected result, or a corrected result, according to the context (JCGM 200:2008 § 2.9).⁴

measurement trueness/trueness of measurement/trueness – closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value; **NOTE 1:** Measurement trueness is not a quantity and thus cannot be expressed numerically, but measures for closeness of agreement are given in ISO 5725¹¹; **NOTE 2:** Measurement trueness is inversely related to systematic measurement error, but is not related to random measurement error; **NOTE 3:** Measurement accuracy should not be used for “measurement trueness” and vice versa (JCGM 200:2008 § 2.14).⁴

measurement uncertainty/uncertainty of measurement/uncertainty – non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used; **NOTE 1:** Measurement uncertainty includes components arising from systematic effects, such as components associated with corrections and the assigned quantity values of measurement standards, as well as the definitional uncertainty. Sometimes estimated systematic effects are not corrected for but, instead, associated uncertainty components are incorporated; **NOTE 2:** The parameter may be, for example, a standard deviation (SD) called standard measurement uncertainty (or a specified multiple of it), or the half-width of an interval, having a stated coverage probability; **NOTE 3:** Measurement uncertainty comprises, in general, many components. Some of these may be evaluated by Type A evaluation of measurement uncertainty from the statistical distribution of the quantity values from series of measurements and can be characterized by SDs. The other components, which may be evaluated by Type B evaluation of measurement uncertainty, can also be characterized by SDs, evaluated from probability density functions based on experience or other information (JCGM 200:2008 § 2.26).⁴

measuring interval/working interval – set of values of quantities of the same kind that can be measured by a given measuring instrument or measuring system with specified instrumental uncertainty, under defined conditions; **NOTE 1:** The lower limit of a measuring interval should not be confused with detection limit; **NOTE 2:** In some fields, the term is “measuring range” or “measurement range,” but this usage should be discouraged (JCGM 200:2008 § 4.7)⁴; **EXAMPLE:** The measuring interval $r[a;b]$ has the measuring range $b - a$ (JCGM 200:2008).⁴

measuring system – set of one or more measuring instruments and often other devices, including any reagent and supply, assembled and adapted to give information used to generate measured quantity values within specified intervals for quantities of specified kinds (JCGM 200:2008 § 3.2).⁴

metrological traceability – property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty; **NOTE 1:** For this definition, a “reference” can be a definition of a measurement unit through its practical realization, or a measurement procedure including the measurement unit for a nonordinal quantity, or a measurement standard; **NOTE 2:** Metrological traceability requires an established calibration hierarchy; **NOTE 3:** Metrological traceability of a measurement result does not ensure that the measurement uncertainty is adequate for a given purpose or that there is an absence of mistakes; **NOTE 4:** A comparison between two measurement standards may be viewed as a calibration if the comparison is used to check and, if necessary, correct the quantity value and measurement uncertainty attributed to one of the measurement standards (JCGM 200:2008 § 2.41).⁴

nominal property – property of a phenomenon, body, or substance, where the property has no magnitude; **NOTE:** A nominal property has a value, which can be expressed in words, by alphanumerical codes, or by other means; **EXAMPLE 1:** Sex of a human being; **EXAMPLE 2:** Color of a spot test in chemistry; **EXAMPLE 3:** Sequence of amino acids in a polypeptide; **EXAMPLE 4:** Blood group (JCGM 200:2008 § 1.30).⁴

ordinal quantity – quantity, defined by a conventional measurement procedure, for which a total ordering relation can be established, according to magnitude, with other quantities of the same kind, but for which no algebraic operations among those quantities exist; **NOTE 1:** Ordinal quantities can enter into empirical relations only. Differences and ratios of ordinal quantities have no physical meaning; **NOTE 2:** Ordinal quantities are arranged according to ordinal quantity-value scales (JCGM 200:2008 § 1.26)⁴; **EXAMPLE 1:** +, ++, +++ for arbitrary mass concentration of protein in urine; **EXAMPLE 2:** Urine protein amount-of-substance concentration expressed as 0, 1, 2, or 3 with reference to a measurement procedure.

output quantity in a measurement model//output quantity – quantity, the measured value of which is calculated using the values of input quantities in a measurement model (JCGM 200:2008 § 2.51).⁴

property – inherent state- or process-descriptive feature of a system including any pertinent components; **NOTE 1:** A process of a system may be internal or involve the environment; **NOTE 2:** “Quantity” and “nominal property” are specific concepts under the general generic concept “property”; “quantity” is related to magnitude whereas “nominal property” has no such relation (IUPAC § 5.5).¹²

quantity – property of a phenomenon, body, or substance, where the property has a magnitude that can be expressed as a number and a reference; **NOTE 1:** A reference can be a measurement unit, a measurement procedure, a reference material, or a combination of such; **NOTE 2:** The preferred IUPAC/IFCC format for designations of quantities in laboratory medicine is “System—Component; kind of quantity”; **EXAMPLE:** “Plasma (Blood)-Sodium ion; amount-of-substance concentration equal to 143 mmol/L in a given person at a given time”; **NOTE 3:** The term “quantity” should not be confused with the term “amount.” The term “quantity” is often used for “kind of quantity” (JCGM 200:2008 § 1.1).⁴

quantity value//value of a quantity//value – number and reference together expressing magnitude of a quantity; **NOTE:** According to the type of reference, a quantity value is either:

- A product of a number and a measurement unit; the measurement unit one is generally not indicated for quantities of dimension one,
- A number and a reference to a measurement procedure, or
- A number and a reference material (measurement standard, calibrator);

EXAMPLE: Arbitrary amount-of-substance concentration of lutropin in a given sample of plasma (World Health Organization International Standard 80/552): 5.0 International Unit/L (modified from JCGM 200:2008 § 1.19).⁴

random measurement error//random error of measurement//random error – component of measurement error that in replicate measurements varies in an unpredictable manner; **NOTE 1:** A reference quantity value for a random measurement error is the average that would ensue from an infinite number of replicate measurements of the same measurand; **NOTE 2:** Random measurement errors of a set of replicate measurements form a distribution that can be summarized by its expectation, which is generally assumed to be zero, and its variance; **NOTE 3:** Random measurement error equals measurement error minus systematic measurement error (JCGM 200:2008 § 2.19)⁴; **NOTE 4:** The standard deviation of the random measurement error is sometimes called *imprecision*.

relative standard measurement uncertainty – standard measurement uncertainty divided by the absolute value of the measured quantity value different from zero (modified from JCGM 200:2008 § 2.32)⁴; **NOTE 1:** The relative standard measurement uncertainty of a quantity x is formally symbolized $u(x)/|x|$; **NOTE 2:** When the relative standard measurement uncertainty is expressed in percentage form, $100 \times u(x)/|x|$, it can be symbolized $\%u(x)$.

repeatability condition of measurement//repeatability condition – condition of measurement, out of a set of conditions that includes the same measurement procedure, same operators, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time (JCGM 200:2008)⁴; **NOTE:** In chemistry, the term “within-run,” or “intraserial,” or “intrarun precision condition of measurement” is sometimes used to designate this concept (modified from JCGM 200:2008 § 2.20).⁴

reproducibility condition of measurement//reproducibility condition – condition of measurement, out of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects; **NOTE 1:** The different measuring systems may use different measurement procedures; **NOTE 2:** A specification should give the conditions changed and unchanged, to the extent practical (JCGM 200:2008 § 2.24)⁴; **NOTE 3:** In chemistry, the terms “between-laboratories,” “interlaboratory,” or “among-laboratories precision condition of measurement” are sometimes used to designate this concept.

run – series of measurements within which the trueness and precision of the measuring system are expected to be stable; **NOTE 1:** In a series of observations, the occurrence of an uninterrupted series of the same quantity is called a “run”; **NOTE 2:** Between analytical runs, events may occur that render the measurement process susceptible to important variations.

sample – one or more parts taken from a system, and intended to provide information on the system, often to serve as a basis for decision on the system or its production (ISO 15189)¹³; **EXAMPLE 1:** A volume of serum taken from a larger volume of serum; **EXAMPLE 2:** An unbiased or randomly selected subset of a population of measurement results.

selectivity of a measuring system//selectivity – property of a measuring system, used with a specified measurement procedure, whereby it provides measured quantity values for one or more measurands such that the values of each measurand are independent of other measurands or other quantities in the phenomenon, body, or substance being investigated; **NOTE:** Selectivity is a concept close to analytical specificity; **EXAMPLE 1:** Capability of a measuring system including a mass spectrometer to measure the ion current ratio generated by two specified compounds without disturbance by other specified sources of electric current; **EXAMPLE 2:** Capability of a measuring system to measure the power of a signal component at a given frequency without being disturbed by signal components or other signals at other frequencies; **EXAMPLE 3:** Capability of a measuring system to measure the amount-of-substance

concentration of creatinine in blood plasma by a Jaffe procedure without being influenced by the glucose, urate, ketone, and protein concentrations (JCGM 200:2008 § 4.13).⁴

series – a delineated set of measured samples; **NOTE:** The series can be defined differently depending on the measurement system, eg, between calibrations, or reagent lots, within a defined time interval.¹⁴

standard deviation (SD) – the positive square root of the variance ($V(X)$): $\sigma = \sqrt{V(X)}$ (ISO 3534-1 § 1.23)⁹; **NOTE:** The SD of the quantity x is symbolized s_x or $s(x)$.

standard measurement uncertainty//standard uncertainty of measurement//standard uncertainty – measurement uncertainty expressed as a standard deviation (JCGM 200:2008 § 2.30)⁴; **NOTE 1:** The standard measurement uncertainty of the quantity x is symbolized u_x or $u(x)$; **NOTE 2:** The square of the standard measurement uncertainty of the quantity x is symbolized u_x^2 or $u^2(x)$.

system – part or phenomenon of the perceivable or conceivable world consisting of a demarcated arrangement of a set of elements and a set of relationships or processes between these elements; **NOTE:** The concept “system” is used both in the sense of a phenomenon, body, or substance, such as a person or a blood sample, carrying a property, and in the combination of measuring instruments, reagents, and supplies constituting a measuring system (IUPAC § 3).¹²

systematic measurement error//systematic error of measurement//systematic error – component of measurement error that in replicate measurements remains constant or varies in a predictable manner; **NOTE 1:** A reference quantity value for a systematic measurement error is a true quantity value, or a measured quantity value of a measurement standard of negligible measurement uncertainty, or a conventional quantity value; **NOTE 2:** Systematic measurement error, and its causes, can be known or unknown. A correction can be applied to compensate for a known systematic measurement error; **NOTE 3:** Systematic measurement error equals measurement error minus random measurement error (JCGM 200:2008 § 2.17)⁴; **NOTE 4:** “Measurement bias” is an estimate of “systematic measurement error.”

true quantity value//true value of a quantity//true value – quantity value consistent with the definition of a quantity (JCGM 200:2008 § 2.11)⁴; **NOTE 1:** When the definitional uncertainty associated with the measurand is considered to be negligible compared to the other components of the measurement uncertainty, the measurand may be considered to have an “essentially unique” true quantity value. This is the approach taken by the GUM¹ and associated documents, where the word “true” is considered to be redundant (JCGM 200:2008)⁴; **NOTE 2:** For most measurands, there is no single true quantity value but rather a set of true quantity values consistent with the definition; they are expressed as a definitional uncertainty associated with a measured quantity value. If the definitional uncertainty is considered to be negligible compared to the other components of a measurement uncertainty, the measurand may be considered to have an “essentially unique” true quantity value.

Type A evaluation of measurement uncertainty//Type A evaluation – evaluation of a component of measurement uncertainty by a statistical analysis of measured quantity values obtained under defined measurement conditions; **NOTE 1:** For various types of measurement conditions, see **repeatability condition of measurement** and **reproducibility condition of measurement** (JCGM 200:2008 § 2.28)⁴; **NOTE 2:** Although Type A and Type B evaluations are treated the same mathematically, in applications for clearance or approval of devices by regulatory agencies, Type A evaluations are generally preferred when they are practical.

Type B evaluation of measurement uncertainty//Type B evaluation – evaluation of a component of measurement uncertainty determined by means other than a Type A evaluation of measurement uncertainty (JCGM 200:2008 § 2.29)⁴; **EXAMPLES:** Evaluation based on information:

- Associated with authoritative published quantity values,
- Associated with the quantity value of a certified reference material,
- Obtained from a calibration certificate,
- About drift,
- Obtained from the accuracy class of a verified measuring instrument,
- Obtained from limits deduced through personal experience (JCGM 200:2008)⁴;

NOTE: Although Type A and Type B evaluations are treated the same mathematically, in applications for clearance or approval of devices by regulatory agencies, Type A evaluations are generally preferred when they are practical.

uncertainty budget – statement of a measurement uncertainty, of the components of that measurement uncertainty, and of their calculation and combination (JCGM 200:2008 § 2.33)⁴; **NOTE:** An uncertainty budget should include the measurement model, estimates, and measurement uncertainties associated with the quantities in the measurement model, covariances, type of applied probability density functions, degrees of freedom, type of evaluation of measurement uncertainty, and any coverage factor (JCGM 200:2008 § 2.33).⁴

validation – verification, where the specified requirements are adequate for an intended use; **EXAMPLE:** A measurement procedure, ordinarily used for the measurement of mass concentration of nitrogen in water, may be validated also for measurement in human serum (JCGM 200:2008 § 2.45)⁴; **NOTE:** The intended use or user's needs are external to the measuring system and independent of it, whereas a performance characteristic is part of the measuring system or measurement procedure, ie, it is internal to the measuring system (verification).

variance – the expectation of the square of the centered random variable (ISO 3534-1 § 1.22)⁹; **NOTE:** The expected variance of measurements of the quantity x is symbolized σ_x^2 or $\sigma^2(x)$.

verification – provision of objective evidence that a given item fulfills specified requirements (JCGM 200:2008)⁴; **EXAMPLE:** Confirmation that performance properties or legal requirements of a measuring system are achieved (JCGM 200:2008)⁴; **NOTE 1:** The item may be, eg, a process, measurement procedure, material, compound, or measuring system (JCGM 200:2008)⁴; **NOTE 2:** The specified requirements may be, eg, that a manufacturer's specifications are met (JCGM 200:2008)⁴; **NOTE 3:** In chemistry, verification of the identity of the entity involved, or of activity, requires a description of the structure or properties of that entity or activity (JCGM 200:2008).⁴

3.4 Abbreviations and Acronyms

%CV	coefficient of variation expressed in percent
A _{1C}	glycated hemoglobin
AG	average glucose
ANOVA	analysis of variance
BIPM	Bureau International des Poids et Mesures
CEN	Comité Européen de Normalisation; European Committee for Standardization
CRM	certified reference material
eAG	estimated average glucose
GUM	<i>Guide to the expression of uncertainty in measurement</i>
IEC	International Electrotechnical Commission
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IQC	internal quality control
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry

IVD	<i>in vitro</i> diagnostic
LL	lower-bound limit
MD	minimal difference
NIST	National Institute of Standards and Technology
Pt	patient system
QC	quality control
RCV	reference change value
SD	standard deviation
UL	upper-bound limit
VIM	Vocabulaire International de Métrologie; <i>International vocabulary of basic and general terms in metrology</i>

3.5 Symbols

The following are mathematical definitions for concepts used in this document. The following symbols represent:

$\text{cov}(x,y)$	covariance of quantities x and y
k	coverage factor
df	degrees of freedom
m	the number of groups of values (eg, separate runs)
$N(\bar{x}, s^2(x))$	normal distribution with mean $(\bar{x})$ and variance s^2
n	the total number of values
n_i	the number of values in the i^{th} group
$r(x,y)$	correlation coefficient for quantities x and y
SD	standard deviation
SS	sum of squares
$s(x)$	standard deviation of x
$s(\bar{x})$	standard deviation of the mean//standard error of the mean//standard error
$U(x)$	expanded uncertainty, equal to $k \times u_c(x)$
$u_c(x)$	combined uncertainty over multiple individual sources of uncertainty in a measurement system
$u(x)$	the assigned standard uncertainty on the quantity value, akin to standard deviation
x	a measurement quantity value for a measurement
$ x $	absolute value of quantity x
$\bar{x}$	arithmetic mean of a set of data//average
x_i	the i^{th} member of a group of values (eg, repeated measurements of a sample)
x_{ji}	the j^{th} member of the i^{th} group
y	a measurement quantity value for a measurement different from x

3.6 Summary Statistics

3.6.1 Mean of x

$$\bar{x} = \frac{\sum_{i=1}^n x_i}{n} \quad (1)$$

3.6.2 Sample Variance of x

$$s^2(x) = \frac{\sum_i^n (x_i - \bar{x})^2}{n-1} \quad (2)$$

The statistical community tends to work with variances for mathematical convenience. However, the units of $s^2(x)$ are not the same as the x values and thus are less suited to physical interpretation.

3.6.3 Standard Deviation of x

$$s(x) = \sqrt{s^2(x)} = \sqrt{\frac{\sum_i^n (x_i - \bar{x})^2}{n-1}} \quad (3)$$

To the extent that the x values can be considered to be an independent, identically distributed sample from a roughly normal (gaussian) distribution (denoted $N(.,.)$), the mean and variance of x characterize the distribution of the x values as $N(\bar{x}, s^2(x))$.

3.6.4 Coefficient of Variation//Relative Standard Deviation Expressed as Percent

$$\%CV(x) = 100 \times \frac{s(x)}{|\bar{x}|} \quad (4)$$

For many clinical measurements, standard deviation (SD) increases proportionally with the magnitude of the measured value over the linear portion of the measuring interval. For such measurements, the coefficient of variation expressed in percent ($\%CV(x)$) can be a more convenient summary of expected measurement variability than is $s(x)$ itself.

3.6.5 Standard Deviation of the Mean//Standard Error of the Mean//Standard Error

$$s(\bar{x}) = \frac{s(x)}{\sqrt{n}} \quad (5)$$

The standard deviation of a series of n independent repeated measurements, $s(x)$, usefully summarizes the variability of the population of x values only to the extent that the x values follow a normal (gaussian) distribution. The standard deviation of the mean, $s(\bar{x})$, summarizes the variability of the estimated mean of the x values irrespective of the distribution of the x values themselves.

3.6.6 Pooled Standard Deviation for x Organized Into Subgroups

If the SD is constant in the measuring interval and if the data are organized into groups, the best estimate of the SD is provided by pooling the SDs of the individual groups, $s(x_i)$:

$$s_{\text{pooled}}(x) = \sqrt{\frac{\sum_i^m (n_i - 1) \times s^2(x_i)}{\left(\sum_i^m n_i - m\right)}}. \quad (6)$$

where n is the number of observations in each group and m is the number of groups.

For example, the within-run mean square MS_{wth} described in Section 7.3 is a pooled SD. In the special case in which every group consists of two values (eg, duplicate results for patient samples), this can be simplified as

$$s_{\text{pooled}}(x) = \sqrt{\frac{\sum_i^m d_i^2}{2m}}; \quad d_i = x_{1i} - x_{2i}. \quad (7)$$

3.6.7 Correlation Between x and y

$$r(x, y) = \frac{\sum_i^n (x_i - \bar{x}) \times (y_i - \bar{y})}{\sqrt{\sum_i^n (x_i - \bar{x})^2 \times \sum_i^n (y_i - \bar{y})^2}} \quad (8)$$

The value of $r(x, y)$ measures the strength of the linear association between x and y , ranging from 1 for perfectly correlated values (y increases linearly as x increases) to 0 for completely uncorrelated values (no linear relationship between the values) to -1 for perfectly negatively correlated values (y decreases linearly as x increases).

3.6.8 Covariance of x and y

$$\text{cov}(x, y) = \frac{\sum_i^n (x_i - \bar{x}) \times (y_i - \bar{y})}{n} \quad (9)$$

Covariance is positive if a value x above the mean $\bar{x}$ tends to occur when the value of y is above its mean $\bar{y}$.

3.6.9 Error Propagation

Given a measurement equation that combines two (or more) input measurement values, $z = f(x, y)$, one needs to know how to propagate (combine) the uncertainties of the measured variables, $u(x)$ and $u(y)$, to determine the uncertainty of the desired result: $u_c(z)$. The following illustrate the GUM-recommended¹ method for accomplishing this propagation.

Other well documented computationally intense methods are available.⁴⁷ Although for very complex measurement equations these methods may offer advantages, the following (relatively) simple propagation formulae are adequate in most situations. One should bear in mind, however, that all methods of uncertainty evaluation and error propagation are approximations and that different methods may yield somewhat different estimates.

3.6.9.1 General Formula for Combining Two Terms

Given the equation $z = f(x, y)$, where f is any algebraic function, the first-order Taylor's series approximation for $u_c(z)$ is the rather intimidating

$$u_c(z) = u(f(x, y)) = \sqrt{\left(u(x) \times \frac{\partial z}{\partial x}\right)^2 + \left(u(y) \times \frac{\partial z}{\partial y}\right)^2 + 2 \times \text{cov}(x, y) \times \frac{\partial^2 z}{\partial x \partial y}},$$

where $\partial(z)/\partial(x)$ and $\partial(z)/\partial(y)$ indicate evaluation of the partial derivative of the function with respect to the given term (x or y). The qualifier “first order” signifies that this approximation is quite good for functions that are nearly linear in x and y in the “near neighborhood” of a particular value for z . This approximation is always good for addition and subtraction, and is generally adequate for any smoothly changing function, such as multiplication or division by a value not close to zero. The approximation grows less adequate as the curvature of the function grows larger, such as division by values increasingly close to zero. These first-order equations yield uncertainty estimates that are adequate for most purposes met in the clinical laboratory.

Although the general formula appears daunting, it reduces to tractable forms for the common functions of addition, subtraction, multiplication, and division. This is particularly true when the input values can be assumed to be independent—that is, there is no correlation between the x and the y values, so their covariance, $\text{cov}(x, y)$, is zero.

The assumption of independence among the input variables is generally “true enough” for nonsimultaneous measurements. However, it needs to be carefully evaluated whenever the measurement results are related experimentally (eg, areas of overlapping chromatographic peaks), particularly when the measurement equation uses one or more of the input variables more than once (eg, volumetric dilution—see Example 3 in Section 6.4).

3.6.9.2 Practical Formula for Addition and Subtraction

Given the equation $z = x \pm y$, and assuming that x and y are independently determined,

$$u_c(z) = u(x \pm y) = \sqrt{u^2(x) + u^2(y)}, \quad (10)$$

where $\pm$ indicates that the equation applies to both addition (+) and subtraction (−).

If x and y are significantly correlated, then $\text{cov}(x, y)$ will not be zero and the following full form of the propagation formula is required:

$$\begin{aligned} u_c(z) &= u(x \pm y) = \sqrt{u^2(x) + u^2(y) \pm 2 \times \text{cov}(x, y)} \\ &= \sqrt{u^2(x) + u^2(y) \pm 2 \times u(x) \times u(y) \times r(x, y)}. \end{aligned} \quad (10a)$$

Consider estimating the uncertainty of the difference between two independent results A and B with the same uncertainty $u(A)$: the function is $z = A - B$ and Equation 10 yields

$$u(A - B) = \sqrt{u^2(A) + u^2(A)} = \sqrt{2 \times u^2(A)} = \sqrt{2} \times u(A).$$

However, if A and B were perfectly correlated so that $r(A,B) = 1$, and thus should not be ignored, then Equation 10a yields

$$u(A-B) = \sqrt{u^2(A) + u^2(A) - 2 \times u(A) \times u(A) \times r(A,B)} = \sqrt{2 \times u^2(A) - 2 \times u^2(A) \times 1} = 0.$$

If instead, the uncertainty of the sum of A and B , leading to the function $z = A + B$, were considered, then the above expressions would be:

$$u(A+B) = \sqrt{u^2(A) + u^2(A)} = \sqrt{2 \times u^2(A)} = \sqrt{2} \times u(A) \text{ and}$$

$$u(A+B) = \sqrt{u^2(A) + u^2(A) + 2 \times u(A) \times u(A) \times r(A,B)} = \sqrt{2 \times u^2(A) + 2 \times u^2(A) \times 1} = 2 \times u(A).$$

3.6.9.3 Practical Formula for Multiplication and Division

Given the equation $z = x \times y$ or $z = x/y$, and assuming that x and y are independently determined,

$$\frac{u_c(z)}{|z|} = \frac{u(x \times y)}{|x \times y|} \text{ or } \frac{u(x/y)}{|x/y|} = \sqrt{\left(\frac{u(x)}{x}\right)^2 + \left(\frac{u(y)}{y}\right)^2}, \quad (11)$$

where $|z|$ indicates taking the absolute value of the function, reminding us that uncertainties must never be smaller than zero.

If x and y are significantly correlated, then $\text{cov}(x,y)$ will not be zero and the full forms of the propagation formula are required. The formula for multiplication is

$$\begin{aligned} \frac{u_c(z)}{|z|} &= \frac{u(x \times y)}{|x \times y|} = \sqrt{\left(\frac{u(x)}{x}\right)^2 + \left(\frac{u(y)}{y}\right)^2 + 2 \times \frac{\text{cov}(x,y)}{x \times y}} \\ &= \sqrt{\left(\frac{u(x)}{x}\right)^2 + \left(\frac{u(y)}{y}\right)^2 + 2 \times \frac{u(x)}{x} \times \frac{u(y)}{y} \times r(x,y)} \end{aligned} \quad (11a)$$

and the formula for division is

$$\begin{aligned} \frac{u_c(z)}{|z|} &= \frac{u(x/y)}{|x/y|} = \sqrt{\left(\frac{u(x)}{x}\right)^2 + \left(\frac{u(y)}{y}\right)^2 - 2 \times \frac{\text{cov}(x,y)}{x \times y}} \\ &= \sqrt{\left(\frac{u(x)}{x}\right)^2 + \left(\frac{u(y)}{y}\right)^2 - 2 \times \frac{u(x)}{x} \times \frac{u(y)}{y} \times r(x,y)} \end{aligned} \quad (11b)$$

Consider multiplication or division of the independent results A and B , both having the same uncertainty $u(A)$. Equation 11 yields

$$\frac{u(A \times B)}{A \times B} = \frac{u(A/B)}{A/B} = \sqrt{\left(\frac{u(A)}{A}\right)^2 + \left(\frac{u(A)}{B}\right)^2} = u(A) \times \sqrt{\frac{1}{A^2} + \frac{1}{B^2}}.$$

However, if A and B were again perfectly correlated so that $r(A,B) = 1$, and thus should not be ignored, for the multiplication function $z = A \times B$, Equation 11a yields

$$\frac{u(A \times B)}{A \times B} = \sqrt{\left(\frac{u(A)}{A}\right)^2 + \left(\frac{u(B)}{B}\right)^2 + 2 \times \frac{u(A)}{A} \times \frac{u(B)}{B} \times r(A,B)} = u(A) \times \sqrt{\left(\frac{1}{A} + \frac{1}{B}\right)^2},$$

and for the division function $z = A/B$, Equation 11b yields

$$\frac{u(A/B)}{A/B} = \sqrt{\left(\frac{u(A)}{A}\right)^2 + \left(\frac{u(B)}{B}\right)^2 - 2 \times \frac{u(A)}{A} \times \frac{u(B)}{B} \times r(A,B)} = u(A) \times \sqrt{\left(\frac{1}{A} - \frac{1}{B}\right)^2}.$$

While measurements in laboratory practice generally involve more than two input values, error propagation can generally be accomplished through a series of binary combinations. Examples 1 and 2 in Section 6.4 exemplify the tractable formula for simple addition/subtraction and multiplication/division. Example 3, also in Section 6.4, exemplifies the more general situation in which the tractable formulae are applied in series.

3.6.10 Expanded Uncertainty

$$U(x) = k \times u_c(x) \quad (12)$$

The combined standard uncertainty, $u_c(x)$, can be considered as the “SD” estimate for the variability of a bias-corrected result x . It is common metrological practice to assert that the interval $x \pm 2 \times u_c(x)$ includes the true value of x with approximately a 95% level of confidence, and that $x \pm 3 \times u_c(x)$ includes the true value with about a 99% level of confidence. Underlying these levels of confidence are the assumptions that:

- The distribution of x is normal.
- $u_c(x)$ has been quite well established, typically by evaluation of a large number of independent measurements, where “large” is a somewhat subjective concept but often taken to be anything greater than 10.

When $u_c(x)$ is not based on a large number of measurements, then the coverage factor, k , needed to achieve a defined level of confidence must be otherwise estimated, eg, from the Student t distribution. The coverage level of confidence, p , associated with the $U(x)$ should always be specified, either in words or using the notation $U_p(x)$.

4 Strategies to Estimate Measurement Uncertainty

This document illustrates how the “top-down” approach can estimate the measurement uncertainty attributed to the instrument, reagent, and personnel variables from the long-term QC data routinely collected in most laboratories. This document also illustrates how the “bottom-up” approach can be used to obtain uncertainty estimates from assay performance data collected in the verification experiments and information provided by manufacturers and in the published literature.

Two examples of how this information can be used are:

- Ensuring that measurement uncertainty meets clinical requirements
- Identifying sources of variation in results that can potentially be reduced

4.1 Potential Sources of Measurement Uncertainty

Most laboratories use a combination of fully automated commercial measurement systems and less automated assays developed using components and instruments purchased from various sources. Both types of assays have multiple sources of variation, some that are inherent in the purchased products and some that are caused by laboratory procedures and personnel.

Examples of sources of measurement uncertainty inherent in purchased equipment are:

- Volumetric mechanisms, eg, pipettes
- Signal detectors
- Calibration and data reduction curve-fitting algorithms
- Instrument drift over time
- Differences between instruments
- Sample carryover
- Reagent carryover

Examples of sources of measurement uncertainty associated with purchased reagents are:

- Assigned value of calibrators
- Lot-to-lot variations in reagent response
- Stability of reagents and calibrators
- Commutability of calibrators and reference materials

Examples of activities associated with measurement procedures that can affect measurement uncertainty are:

- Frequency of calibration
- Maintenance

Examples of sources of measurement uncertainty associated with laboratory personnel are:

- Deficiencies in education and training
- Lack of compliance with procedures/instructions
- Lack of manual dexterity, eg, pipetting

4.2 Use of Readily Available Data

The uncertainty inherent in a measurement procedure can be assessed in various ways. A straightforward approach is to design an experiment in which patient samples and/or control materials are measured repeatedly under defined conditions (see CLSI documents C24,¹⁵ EP05,¹⁶ EP06,¹⁷ EP09,¹⁸ EP10,¹⁹ and EP15,²⁰ as well as ISO 21748³ and ISO TS 21749²). However, the routine QC and method verification data collected by most laboratories contain valuable information for understanding and controlling measurement uncertainty. For example, most laboratories repeatedly measure control specimens at multiple concentrations. These data provide an immediate assessment of variability at the particular concentrations. When such data are collected over a sufficiently long period of time, they may be used to identify and quantify sources of measurement uncertainty that influence the measurement system. The variability of these influences over a defined period of time, typically estimated as SDs, can be used to estimate the combined standard uncertainty (u_c). It should be recognized that the standard uncertainty obtained from control materials may differ from that using patient materials.

If suitable identifiers, eg, instrument number, reagent lot number, calibrator number, and other operational parameters, are attached to the results of the measurements of the control samples, statistical techniques can be used to estimate the measurement uncertainty associated with each of these variables. Similarly, the verification data collected when procedures are implemented can be used to estimate some of the components of assay variability.³

An estimate of the measurement uncertainty of results produced by a routine measuring system is an essential part of the verification of its performance. Estimating measurement uncertainties may also provide laboratories with a better understanding of the performance and limitations of their methods and, thereby, identify technical steps in which uncertainty potentially can be reduced. By making measurement uncertainty information available to clinical users, laboratories can contribute to improved interpretation of patient results because such data are essential for rational comparison of results with clinical decision limits and previous patient results. Meeting ISO accreditation standards requires that measurement uncertainties be estimated when practical. Both ISO 15189¹³ and ISO/IEC 17025²¹ cite the GUM¹ as one model for estimating uncertainty, although other models exist and may be used.²²

For manufacturers of reagents and instruments and other providers of measurement methods, estimating the magnitude of various sources of measurement uncertainty and how they contribute to a target allowable uncertainty can help guide the development of new measurement methods. The evaluation of the overall uncertainty of the measurement is an essential aspect of demonstrating that it is suitable for its intended purpose. Therefore, estimation of measurement uncertainty is an essential component of the specification of IVD devices by manufacturers.

4.3 Combining Random and Systematic Measurement Errors: Two Approaches

Laboratory measurements are subject to random error and systematic error. Random error refers to the random scatter, or imprecision, of repeated measurements (see CLSI documents EP05¹⁶ and EP15²⁰). Systematic error, or bias, is the difference between the mean of the measured quantity values and the assumed true value for that quantity. (See Section 8 and CLSI documents EP09¹⁸ and EP15.²⁰) Bias of a particular measurement procedure may vary over time, eg, depending on variation in calibrators and reagent lots. Taking a long-term view, some short-term bias may reasonably be regarded as random variation.

The measurement uncertainty approach to quantifying measurement variability is relatively new to the field of laboratory medicine. The “uncertainty model” provides a slightly different view of the nature of measurement results than the traditional “error model” does, and attempts to combine random and systematic errors into one concept.²³ The major distinguishing characteristics of the two models are summarized below.

4.3.1 “Error Model”

The “error model”:

- Regards the true value of a measurement to be a single unknowable quantity value
- Treats random and systematic errors separately
- Applies to a single measured quantity value

Traditionally, a so-called *total error* for a measured quantity value is the calculated sum of two terms. The first term, the total systematic measurement error, is based on observations or literature and expressed as the mean of the difference between observed values and the reference or target value. The second term is an estimate of the random measurement variation, ie, the SD of the observed differences multiplied by a coverage factor, according to the desired level of confidence. The sum of the two terms is an upper limit on the total error of a measurement, assuming random error follows a gaussian distribution.

The *total error* model is described in detail in CLSI document EP21,²⁴ which also provides a nonparametric approach. CLSI document EP21²⁴ emphasizes that all sources of assay error be included using a data collection protocol that is representative of routine assay use.

If a quantity for which a total error was calculated is used as input to another measurement, the total error has to be separated into its systematic and random components before they can be combined with those of the other input quantities in a measurement model. This lack of transferability is an important drawback of the error model.

4.3.2 “Uncertainty Model”

The “uncertainty model”:

- Defines an interval within which the true value of the measurement is expected to lie with a stated level of confidence
- Assumes that all significant systematic errors can be identified and corrected within some defined uncertainty so that all uncertainty components can be treated in the same manner
- Applies to all measured quantity values obtained by a given measurement system
- Allows the laboratory to report the bias (and its associated uncertainty, if known), along with any uncorrected result, if a laboratory decides not to correct for known bias, for instance, to comply with applicable local, regional, or national regulations.
- Can be extended to resolve the suspected but unconfirmed bias components²⁵

The uncertainty model is described in detail in the GUM¹ and also discussed in another publication.²⁶

The “uncertainty model” corrects for the known biases and combines the uncertainties of these corrections with the uncertainty due to the components of random error. The associated uncertainty interval will be wider than that estimated from only the random sources of uncertainty. This approach of combining the errors is illustrated in Figure 1.

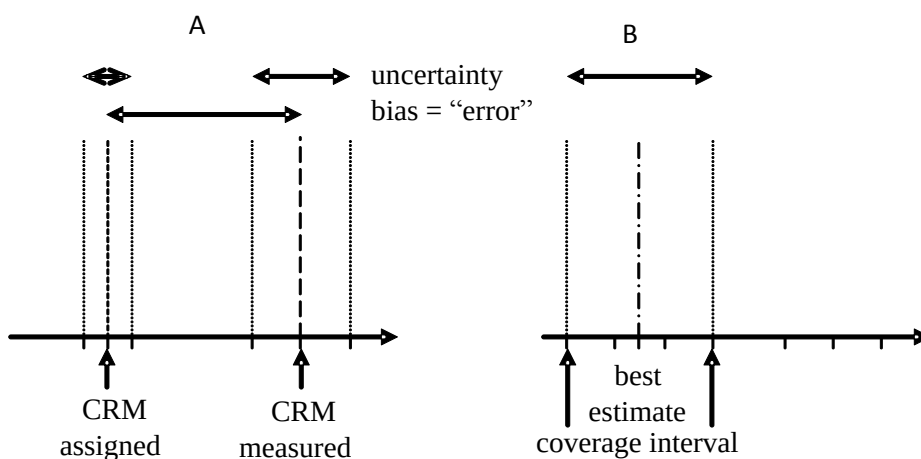


Figure 1. Uncertainty Model Approach to Combining Random and Systematic Errors. A) The measured quantity value of a certified reference material (CRM) is corrected giving B) an estimate of the quantity value with an increased uncertainty. The estimate of the quantity value coincides with the assigned value of the CRM after bias correction. The “best estimate” will be within the coverage interval with a stated level of confidence (p). The coverage interval is recognized as the estimate of the expanded

uncertainty, U , which is the combined uncertainty multiplied by a coverage factor, k (see Section 3.6.10). In the first row of Figure 1, arrows indicate the uncertainty of the CRM assigned value and the uncertainty of the measurement quantity value. In the second row, arrows indicate the bias as the difference between the measured value and the CRM assigned value. See Section 8.3 for a numerical example.

5 Overview of Measurement Uncertainty

Measurement uncertainty can be estimated by two different approaches:

- The bottom-up modeling approach is based on a careful, comprehensive dissection of the measurement in which each potential source of uncertainty is identified and quantified. 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. The identified uncertainties are then mathematically combined to generate the “combined standard uncertainty” of the result. This approach is often referred to as the GUM approach.¹
- The top-down modeling approach uses statistical principles to directly estimate the overall uncertainty of a given measuring system, typically by evaluation of experimental data from special protocols, QC data, or data from a method verification experiment (ISO 21748³).

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 bottom-up procedure may be more useful during method development and top-down for characterizing developed methods or verification. Ideally, the uncertainty estimated by the top-down and bottom-up approaches should be interchangeable.

In both cases, bias needs to be addressed separately and the uncertainty in the estimate of bias, depending on its magnitude relative to other sources, included in the combined uncertainty. Whichever method is used, a first step is to identify the measurand, ie, the quantity that the procedure intends to measure. This can be straightforward and uncomplicated, but in many cases, a quantity is measured that is not the true intended quantity (see Section 3.2).

5.1 Introduction to Terminology of Measurement Uncertainty

Consider the estimation of 24-hour urine total protein using the equation:

$$\{U-Protein_{total}\} = 24 \times \frac{\{U-Protein\} \times \{U-Volume\}}{Time \quad (h)}, \quad (13)$$

where $U-Protein$ is the concentration of protein in the collected urine, $U-Volume$ is the volume of urine collected over a given period of time, $Time$ is the period of time over which the urine was collected, and $U-Protein_{total}$ is the expected amount of protein excreted in urine over a 24-hour period.

Using their formal designations:

- Equation 13 is the measurement function.
- $\{U-Protein\}$, $\{U-Volume\}$, and $Time$ are input quantities to the measurement function.
- $\{U-Protein_{total}\}$ is the output quantity of the measurement function.

Estimating the expected uncertainty associated with $\{U-Protein_{total}\}$ requires knowledge of the uncertainty associated with each of the input quantities. When expressed in the form of SDs, the uncertainties associated with the input quantities are termed *standard uncertainties* and are symbolized $u(x)$. Here, $u(U-Protein)$ is the uncertainty in the protein concentration, $u(U-Volume)$ is the uncertainty in the urine

volume, and $u(\text{Time})$ is the uncertainty in the collection time. The constant factor 24 has, by definition, no associated uncertainty.

These $u(x)$ values can be estimated by different methods, as described below. The $u(x)$ is propagated through the measurement function according to certain rules (see Section 3.6.9) to yield the *combined standard uncertainty* of the result, designated $u_c(y)$, where here y symbolizes $U\text{-Protein}_{\text{total}}$ and $u_c(U\text{-Protein}_{\text{total}})$ is the combined standard uncertainty of the 24-hour urine total protein measurement.

The combined uncertainty can be used to construct an interval of values, centered on the measured (best estimate) value, within which the true value is expected to lie with a stated probability. To reach a level of confidence corresponding to a specified probability, the combined uncertainty is multiplied by a *coverage factor*, k . The uncertainty thus obtained is called the *expanded uncertainty*: $U(y) = \pm k \times u_c(y)$. It is conventional to assert that $k = 2$ provides an approximate 95% level of confidence that the true quantity value is expected to lie in the interval $y = \pm k \times u_c(y)$.

Here, $\{U\text{-Protein}_{\text{total}}\} \pm 2 \times u_c(U\text{-Protein}_{\text{total}}) = \{U\text{-Protein}_{\text{total}}\} \pm U(U\text{-Protein}_{\text{total}})$ is expected to include the true value of the 24-hour urine total protein with about 95% confidence. A higher level of confidence is obtained by a larger coverage factor.

6 Bottom-up Uncertainty Estimation

The bottom-up uncertainty model is formally described in the GUM,¹ and relevant applications are presented in several other documents, eg, the Eurachem/Cooperation on International Traceability in Analytical Chemistry document, *Quantifying Uncertainty in Analytical Measurement*²⁶; National Institute of Standards and Technology (NIST) Technical Note 1297²⁷; and the NIST/SEMATECH Web book.²⁸

The standard uncertainties $u(x)$ can be estimated either by direct experiment (Type A) or from other sources of information (Type B), or a combination of both. The choice depends on the nature of the measurement and the availability of required information.

Type A: an estimate based on statistical analysis of a series of measurements, eg, results from measurements repeated under defined conditions. 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 (see Appendix A).

Both Type A and Type B approaches yield standard uncertainty estimates that can be treated identically when propagated through the measurement function. Ideally, for a given procedure, the measurement uncertainty evaluated using Type A and Type B approaches should give identical results. Note that the distinction between the two approaches is somewhat arbitrary: the result of a Type A evaluation "becomes" a Type B estimate when used for any reason but the original intended purpose. The distinction is made to help evaluate the quality and relevance of the estimate.

6.1 Sources of Uncertainty

The extent to which sources of uncertainty are identified and quantified largely depends on the quality requirements of the users of the measurement results. In laboratory medicine, sources of uncertainty are commonly grouped as affecting the premeasurement, measurement, and postmeasurement phases. This document considers only uncertainty sources that are directly related to the measuring system itself, such as:

- Imprecision (within run, between run, between laboratories, and between instruments)
- Calibration (parameter estimation, model error)
- Trueness of calibrator-assigned values, and commutability of calibrators and reference materials
- Sample-related effects (matrix, interferences)
- Batch differences in reagents, product calibrators, and reference materials
- Differences among operators
- Equipment variability (eg, balances, pipettes, instrument maintenance)
- Environmental variability (eg, temperature, humidity, vibration, voltage)

Also, influence factors, ie, quantities that do not affect the quantity that is actually measured but may affect the relation between the indication and the measurement result, need to be identified. Interferences and other matrix effects are among the more common clinically relevant influence factors. Because influence factors may cause incorrect results, they need to be identified. Some influence factors may not be measurable properties.

Figure 2 illustrates the interactions of the input and influence quantities for the measurement of a 24-hour urine total protein calculation of Equation 13. The basic format of Figure 2 is variously termed “Ishikawa diagram,” “cause-and effect diagram,” or “fish-bone diagram.”

The influence factors for {*Urine-Volume*} in Figure 2 have been intentionally left blank as an instructional exercise for the reader. Factors that readers may want to consider include the definition of a urine collection or a 24-hour urine total protein amount, measurement technique, temperature, pressure, density, completeness of urine collection, and variables that can influence these quantities. A quantitative estimate of the combined uncertainty is given in Example 10 in Section 9.3.4.

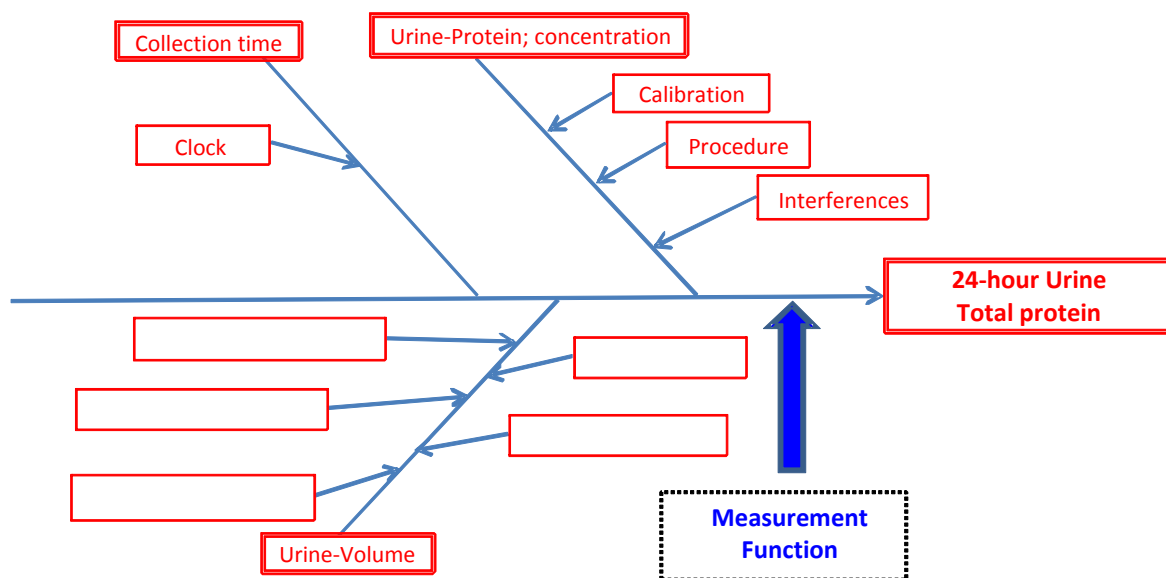


Figure 2. Ishikawa Diagram, Illustrating Input Variables and Some Possible Influence Factors in the Estimation of Urine Total Protein Amount Excreted in 24 Hours. The reader is encouraged to consider what factors should be associated with the empty boxes for urine volume.

Strictly speaking, only uncertainty sources pertaining to the measurement should be included in the measurement uncertainty. However, some or all of the pre- and postmeasurement sources generally have an effect on the reported result and, therefore, potentially on how it is interpreted by the user. Pre- and postmeasurement uncertainties may be difficult to estimate and treat correctly. In laboratory medicine, it is common practice to minimize—where possible—the pre- and postmeasurement uncertainties by

implementing standardized procedures for patient preparation, staff training, specimen collection, transport, storage, and time limit to measurement. It should be noted that a practical premise of the measurement uncertainty concept is that it is assumed that measurements are conducted according to the relevant procedure and without blunders or other technical noncompliances.

6.2 Uncertainty Budget

Once the input quantities and their relationships in a measurement model have been identified, the next step is to establish a list of the sources of uncertainty, their magnitudes as standard uncertainties, and their interactions in the measurement model. The outcome of this exercise is termed an uncertainty budget. Review of the uncertainty budget should check its appropriateness and then be used to help select whether a bottom-up or top-down approach to estimating the combined standard measurement uncertainty of the measurement process is the most appropriate.

For a generic example of a two-point calibration photometric assay, the measurement function is

$$Conc_{\text{sample}} = \left[\frac{S_s - S_0}{S_{\text{cal}} - S_0} \times c_{\text{cal}} \right] \times d + E_m + E_u.$$

An uncertainty budget for this function is given in Table 1.

Table 1. Generic Example of an Uncertainty Budget

Input Quantity	Value	Standard Uncertainty	Relative Uncertainty	Estimate Type*	Source
Sample indication (measurement signal)	S_s	$u(S_s)$	$u(S_s)/ S_s $	Type A	Replication experiment
Calibrator indication (measurement signal)	S_{cal}	$u(S_{\text{cal}})$	$u(S_{\text{cal}})/ S_{\text{cal}} $	Type A	Replication experiment
Blank indication (measurement signal)	S_0	$u(S_0)$	$u(S_0)/ S_0 $	Type B	Previous study
Calibrator concentration	c_{cal}	$u(c_{\text{cal}})$	$u(c_{\text{cal}})/ c_{\text{cal}} $	Type B	Manufacturer
Dilution factor	d	$u(d)$	$u(d)/ d $	Type B	Professional judgment
Matrix effect (eg, interferences)	E_m	$u(E_m)$	$u(E_m)/ E_m $	Type B	Literature
Nonspecified effects	E_u	$u(E_u)$	$u(E_u)/ E_u $	Type B	Professional judgment

* For many components, both Type A and Type B estimates may be plausible.

6.3 Quantification of Uncertainties

Type A uncertainties in Table 1 are typically estimated as the SD of repeated measurements. Type B evaluations are based on literature, professional experience, and so on, and therefore, they may not be directly expressed as standard uncertainties. However, Type B information can be transformed to standard uncertainties by making reasonable assumptions about the nature of the information.

As an example of a simple transformation of Type B information, assume that for Table 1, the manufacturer states the calibrator concentration as $c_{\text{cal}} = X \pm 1\%$ and specifies that this uncertainty provides a 95% level of confidence. Therefore, the relative standard uncertainty for the calibrator is $\pm 0.5\%$ (because $U = k \times u_c$, and $k = 2$, thus $u_c = 1\%/2 = 0.5\%$) or, expressed as a fraction rather than a percent, $u_c = 0.005$. If the manufacturer does not state the coverage probability, then a conservative assumption would be that the stated uncertainty represents u_c and not U , ie, $u_c = 1\% = 0.01$.

See Appendix A for further information on the transformation of some Type B uncertainty specifications.

6.4 Measurement Function and Estimation of the Combined Standard Uncertainty

The measurement function describes mathematically how the input quantities interact to generate the results. The uncertainties of the input variables are propagated according to the measurement function to yield the *combined uncertainty*. Simple propagation rules using the squares of the uncertainties can be applied, provided the input quantities are independent (see Section 3.6.9). The following examples illustrate how the propagation rules are applied to three different common types of measurement function using standard uncertainties (not expanded uncertainties). A simple everyday measurement procedure may serve as an example of the principle.

EXAMPLE 1: Propagation when quantities are added or subtracted in the measurement function

Estimate the uncertainty of combining two independently delivered volumes, V_1 and V_2 , to give a total volume V_3 . The measurement function is

$$V_3 = V_1 + V_2. \quad (14)$$

Following Equation 10 and recognizing that no correlation exists between independent input quantities, the combined uncertainty $u_c(V_3)$ is

$$u_c(V_3) = \sqrt{u^2(V_1) + u^2(V_2)}. \quad (15)$$

Given the input quantity values $V_1 = (100 \pm 0.1)$ mL, and $V_2 = (90 \pm 0.2)$ mL, (ie, $V_1 = 100.0$ mL, $u(V_1) = 0.1$ mL, $V_2 = 90.0$ mL, and $u(V_2) = 0.2$ mL), the output quantity value is $V_3 = 190$ mL with $u_c(V_3) = 0.22$ mL (see Equation 15). With the appropriate rounding (see Section 9.2), the result is $V_3 = (190.0 \pm 0.2)$ mL.

If the input volumes are not independently delivered but perhaps use the same pipette and tip, then V_1 and V_2 are likely to be somewhat positively correlated, that is, $r(V_1, V_2) > 0$. In which case, $u_c(V_3)$ will be somewhat greater than by Equation 15 (the extent of the increase being dependent on the strength of the correlation).

To observe the potential magnitude of this effect, assume that the same pipette and tip are used to deliver two equal volumes over a short period of time so that $V_1 = V_2$, $u(V_1) = u(V_2) = 0.1$, and $r(V_1, V_2) = 1$. Then $u_c(V_3)$ is

$$\begin{aligned} u_c(V_3) &= \sqrt{u^2(V_1) + u^2(V_2) + 2 \times u(V_1) \times u(V_2) \times 1} \\ &= \sqrt{u^2(V_1) + u^2(V_1) + 2 \times u^2(V_1)} = \sqrt{4 \times u^2(V_1)} = 2 \times u(V_1) = 0.20 \text{ mL} . \end{aligned}$$

Whereas if the same volumes with the same $u(V_1) = u(V_2)$ uncertainties were delivered independently, perhaps by different operators using different pipettes, then $r(V_1, V_2) = 0$ and $u_c(V_3)$ would be

$$\begin{aligned} u_c(V_3) &= \sqrt{u^2(V_1) + u^2(V_2) + 2 \times u(V_1) \times u(V_2) \times 0} \\ &= \sqrt{2 \times u^2(V_1)} = \sqrt{2} \times u(V_1) = 0.14 \text{ mL} . \end{aligned}$$

If the same volumes were delivered independently, perhaps by different operators using different pipettes,

but $u(V_1) \neq u(V_2)$, eg, 0.1 and 0.2, respectively, then $r(V_1, V_2) = 0$ and the expanded uncertainty, $U(V_3)$, with a probability defined by a coverage factor k , would be

$$\begin{aligned} U(V_3) &= k \times \sqrt{u^2(V_1) + u^2(V_2) + 2 \times u(V_1) \times u(V_2) \times 0} \\ &= k \times \sqrt{u^2(V_1) + u^2(V_2)} = k \times \sqrt{0.05} = k \times 0.22 \text{ mL} . \end{aligned}$$

EXAMPLE 2: Propagation when quantities are multiplied in the measurement function

Estimate the uncertainty of the amount of protein, $U\text{-Protein}_{\text{amount}}$, in a given collection of urine, $U\text{-Volume}$, of protein concentration $U\text{-Protein}$. The measurement function is

$$\{U\text{-Protein}_{\text{amount}}\} = \{U\text{-Protein}\} \times \{U\text{-Volume}\} . \quad (16)$$

Following Equation 11 and observing that the values of the two dissimilar input quantities are independently determined and thus uncorrelated, the combined uncertainty $u_c(U\text{-Protein}_{\text{amount}})$ is

$$\frac{u_c(U\text{-Protein}_{\text{amount}})}{\{U\text{-Protein}_{\text{amount}}\}} = \sqrt{\left(\frac{u(U\text{-Protein})}{\{U\text{-Protein}\}}\right)^2 + \left(\frac{u(U\text{-Volume})}{\{U\text{-Volume}\}}\right)^2} . \quad (17)$$

Given $\{U\text{-Protein}\} = (150.0 \pm 3.0) \text{ mg/L}$ and $\{U\text{-Volume}\} = (1.500 \pm 0.015) \text{ L}$, then $\{U\text{-Protein}_{\text{amount}}\} = 225.0 \text{ mg}$, $u_c(U\text{-Protein}_{\text{amount}})/\{U\text{-Protein}_{\text{amount}}\} = 0.0224 = 2.24\%$, and $u_c(U\text{-Protein}_{\text{amount}}) = 5.03 \text{ mg}$. With the appropriate rounding (see Section 9.2), the result can be expressed as $\{U\text{-Protein}_{\text{amount}}\} = 225 \text{ mg} \pm 2.2\%$, or $(225 \pm 5) \text{ mg}$.

$$\frac{u_c(U\text{-Protein}_{\text{amount}})}{\{U\text{-Protein}_{\text{amount}}\}} = \sqrt{\left(\frac{3.0}{150.0}\right)^2 + \left(\frac{0.015}{1.5}\right)^2} = 0.0224$$

EXAMPLE 3: Propagation when quantities are added, multiplied, and divided in the measurement function

Estimate the uncertainty of the concentration C_3 after diluting a solution of volume $V_1 = (10 \pm 0.11) \text{ mL}$ and concentration $C_1 = (15 \pm 0.2) \text{ mmol/L}$ with $V_2 = (90 \pm 3) \text{ mL}$ of a solution of concentration $C_2 = (2 \pm 0.1) \text{ mmol/L}$. The measurement function is

$$C_3 = \frac{C_1 \times V_1 + C_2 \times V_2}{V_1 + V_2} , \text{ therefore} \quad (18)$$

$$C_3 = \frac{15 \times 10 + 2 \times 90}{10 + 90} = 3.3 \text{ mmol/L} .$$

Evaluating the uncertainty for this rather more complicated function is less daunting than it may appear because it can be done in a series of simple steps. As shown in Example 1, if the volumes are independent, then the combined uncertainty of the denominator, $denom = V_1 + V_2$, is

$$u_c(denom) = \sqrt{u^2(V_1) + u^2(V_2)} , \text{ therefore} \quad (19)$$

$$u_c(\text{denom}) = \sqrt{0.11^2 + 3.00^2} = 3.00.$$

Again following Equation 11, (see Example 2) and observing that the concentrations and volumes are independent, the relative combined uncertainty of the two terms in the numerator, $C_1 \times V_1$, and $C_2 \times V_2$, are

$$\frac{u_c(C_1 \times V_1)}{|C_1 \times V_1|} = \sqrt{\left(\frac{u(C_1)}{C_1}\right)^2 + \left(\frac{u(V_1)}{V_1}\right)^2} \text{ and } \frac{u_c(C_2 \times V_2)}{|C_2 \times V_2|} = \sqrt{\left(\frac{u(C_2)}{C_2}\right)^2 + \left(\frac{u(V_2)}{V_2}\right)^2}, \text{ therefore} \quad (20)$$

$$\frac{u_c(C_1 \times V_1)}{|C_1 \times V_1|} = \sqrt{\left(\frac{0.2}{15}\right)^2 + \left(\frac{0.11}{10}\right)^2} = 0.02 \text{ and } \frac{u_c(C_2 \times V_2)}{|C_2 \times V_2|} = \sqrt{\left(\frac{0.1}{2}\right)^2 + \left(\frac{3}{90}\right)^2} = 0.06.$$

By rearranging and substituting these two relative uncertainties into Equation 10, the combined uncertainty of the numerator, $num = C_1 \times V_1 + C_2 \times V_2$, is

$$u(num) = \sqrt{(C_1 \times V_1)^2 \times \left(\left(\frac{u(C_1)}{C_1}\right)^2 + \left(\frac{u(V_1)}{V_1}\right)^2\right) + (C_2 \times V_2)^2 \times \left(\left(\frac{u(C_2)}{C_2}\right)^2 + \left(\frac{u(V_2)}{V_2}\right)^2\right)}, \text{ therefore} \quad (21)$$

$$u(num) = \sqrt{150^2 \times 0.02^2 + 180^2 \times 0.06^2} = 11.1.$$

Finally, following Equation 11 and treating the numerator and denominator terms as if they are independent, the relative uncertainty of $C_3 = num/denom$ is

$$\frac{u_c(C_3)}{C_3} = \sqrt{\left(\frac{u(num)}{num}\right)^2 + \left(\frac{u(denom)}{denom}\right)^2}, \text{ therefore} \quad (22)$$

$$\frac{u_c(C_3)}{C_3} = \sqrt{\left(\frac{11.1}{330}\right)^2 + \left(\frac{3}{100}\right)^2} = 0.0451; \quad u_c(C_3) = 0.149 \text{ mmol/L}.$$

Inserting the values of the input quantities into the above formulas, $C_3 = 3.300$ mmol/L, $u(C_3)/|C_3| = 0.0451$, and $u(C_3) = 0.149$ mmol/L. With the appropriate rounding (see Section 9.2), the result can be expressed as $C_3 = 3.30$ mmol/L $\pm$ 4.5% or (3.30 ± 0.15) mmol/L.

However, this uncertainty estimate is somewhat too large. The quantities V_1 and V_2 appear in both the numerator and denominator, and thus num and $denom$ are somewhat positively correlated. Although the mathematical basis for estimating the strength of this correlation is beyond the scope of this document,^a for this example, $r(num, denom) \approx 0.55$ and a less conservative estimate of the relative uncertainty is

$$\frac{u_c(C_3)}{C_3} = \sqrt{0.045^2 - 2 \times \left(\frac{u(num)}{num}\right) \times \left(\frac{u(denom)}{denom}\right) \times 0.55} = 0.0302; \quad u_c(C_3) = 0.10 \text{ mmol/L},$$

^a For this measurement function, $r(num, denom) = \frac{C_1 \times u^2(V_1) + C_2 \times u^2(V_2)}{u(num) \times u(denom)}$.

which, after appropriate rounding, yields $C_3 = 3.30 \text{ mmol/L} \pm 3.0\%$ or $(3.30 \pm 0.10) \text{ mmol/L}$.

6.5 Combining Measurement Uncertainty With Uncertainties From Other Sources

Often the result of a particular measured quantity value, y , may be modified by factors not included in the measurement equation, such as pre- and postanalytical (pre- and postexamination) procedures and sources of biological variation. To the extent that these factors can be identified and the uncertainty attributable to each quantified, an extended function can be defined.

In clinical laboratory medicine as in other areas of chemistry, many effects are proportional to concentration and the extended function involves a series of multiplications^{29,30}:

$$\text{Result} = y \times \text{factor}_1 \times \text{factor}_2 \times \dots \times \text{factor}_n. \quad (23)$$

To the extent that the various factors are independent, following Equation 11, $u_c(\text{Result})$ is

$$\frac{u_c(\text{Result})}{|\text{Result}|} = \sqrt{\left(\frac{u(y)}{y}\right)^2 + \left(\frac{u(\text{factor}_1)}{\text{factor}_1}\right)^2 + \left(\frac{u(\text{factor}_2)}{\text{factor}_2}\right)^2 + \dots + \left(\frac{u(\text{factor}_n)}{\text{factor}_n}\right)^2}. \quad (24)$$

Factors that do not influence the value of the measurement result but do contribute to the uncertainty of the result, such as unknown time since last meal for serum glucose, can be designated as having unit magnitude, $\text{factor}_i = 1$. Factors that do not contribute significant uncertainty, such as the uncertainty in atomic masses due to variability in isotopic abundances for quantities involving molecular weights, can either be excluded from the uncertainty evaluation or assigned to have zero uncertainty, $u(\text{factor}_i) = 0$.

Other effects are added to or subtracted from the measurement result, giving an extended function having the form³¹:

$$\text{Result} = y \pm \text{factor}_1 \pm \text{factor}_2 \pm \dots \pm \text{factor}_n. \quad (25)$$

To the extent that the various factors are independent, following Equation 10, $u_c(\text{Result})$ is

$$u(\text{Result}) = \sqrt{u^2(y) + u^2(\text{factor}_1) + u^2(\text{factor}_2) + \dots + u^2(\text{factor}_n)}. \quad (26)$$

For such an additive function, factors that do not influence the measurement result should be assigned to have a value of zero, $\text{factor}_i = 0$. Factors that do not contribute significant uncertainty should again be excluded from the uncertainty evaluation or assigned to have zero uncertainty, $u(\text{factor}_i) = 0$.

As shown in Example 3, the evaluation of uncertainty for extended models that combine additive and multiplicative factors—although tedious—is relatively straightforward.

7 Top-Down Approach to Estimation of Measurement Uncertainty

7.1 General

In the top-down approach, the combined standard uncertainty of the measurement is directly estimated from repeated measurements of selected samples. This approach is particularly well suited to the closed measuring systems commonly encountered in routine medical laboratories. However, where possible, it is important to develop an uncertainty budget so as to better understand the important sources of uncertainty and their contribution to the combined uncertainty, and to identify opportunities for their reduction or elimination. One such approach applicable to medical laboratories has been proposed.³²

7.2 Assessment of Measurement Uncertainty Using Internal Quality Control Data

Data can be obtained from ongoing internal quality control (IQC) procedures, assuming that QC materials behave like patient samples.³³ 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.

However, collecting results from samples in succession over several runs may lead to overestimating the measurement uncertainty if undue systematic effects occur. On the other hand, recalculating the uncertainty of the IQC 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 overzealous identification and elimination of outliers or excessive trimming of the dataset. Any trimming of the dataset should be carefully justified.

The risk for over- and underestimation of the uncertainty may be minimized by splitting the series of IQC results at times of major changes of materials, reagents, or other measurement conditions and combining estimates made for each of the subsets. This can also be achieved through analysis of variance (ANOVA) components of the data (see Section 7.3).

Note that shifts both large and small occurring at routine changes of conditions can be regarded as systematic errors and, if large, may demand intervention. However, when viewed over the long term, the shifts may be regarded as random variation attributable to ongoing routine changes of conditions rather than bias.

7.3 Analysis of Variance—Variance Components

IQC programs usually comprise measurements of control material of at least two concentrations in each run (arbitrarily defined). If only one measurement of each concentration is obtained in each run, then u_c for each material is just the SD estimated from all results for that material. If more than one measurement of each concentration is performed in each run, then u_c must at least include both within- and between-run components. The magnitudes of these uncertainty components can be estimated using variance component analysis based on ANOVA techniques.

ANOVA procedures are provided in many general purpose data analysis software systems, including spreadsheet programs. These systems vary greatly in their applicability, ranging from very narrow, rigid, and simple to use, to extremely general, flexible, and requiring expert knowledge. However, even the simplest of these systems provides the basic “one-factor” or “one-way” ANOVA suitable for the analysis of data grouped only by run. Typical output from a one-way ANOVA is shown in Example 4.

One need not study or fully understand the mathematics behind the one-way ANOVA to make use of the output. For estimating the magnitude of the within- and between-run uncertainty components, the critical quantities listed in Table 2 are the within-run mean square (MS_{wth}), and the between-run mean square (MS_{btw}). The sum of squares (SS) and degrees of freedom (df) values are intermediate results, and the F and P values indicate the significance of between-run differences.

The within-run SD (s_{wth}) is directly estimated from the listed MS_{wth} value:

$$s_{\text{wth}} = \sqrt{MS_{\text{wth}}} . \quad (27)$$

The between-run SD (s_{btw}) is estimated from the listed MS_{btw} and MS_{wth} and a value, n_0 , related to the number of data values available for each of the m runs included in the following analysis:

$$s_{\text{btw}} = \sqrt{\text{MAX}\left(0, \frac{MS_{\text{btw}} - MS_{\text{wth}}}{n_0}\right)}, \quad (28)$$

where $\text{MAX}(a,b)$ is the function “take the maximum of a and b .” Thus, if $MS_{\text{btw}} < MS_{\text{wth}}$, then $s_{\text{btw}} = 0$. When all runs have the same number of data values, the dataset is said to be “balanced,” and n_0 is the number of data values within each run. Otherwise, a formula is used to calculate n_0 .^b

From the experimental design, the uncertainties s_{wth} and s_{btw} are independent and the combined uncertainty, u_c , appropriate for a single measurement of a given control material is

$$u_c = \sqrt{s_{\text{wth}}^2 + s_{\text{btw}}^2}. \quad (29)$$

The uncertainty associated with the mean, $\bar{x}$, of all the measurements included in a one-way ANOVA is also of interest for bias correction (see Example 6a, Section 8.3.2). When $s_{\text{btw}} > 0$, the uncertainty of the mean is

$$u_c(\bar{x}) = \sqrt{\frac{MS_{\text{btw}}}{n_{\text{total}}}}, \quad (30)$$

where n_{total} is the total number of measurements used in the analysis; when $s_{\text{btw}} = 0$, the assumptions of the one-way ANOVA model are not met, and Equation 5 provides the more appropriate estimate:

$$u_c(\bar{x}) = s(\bar{x}) = \frac{s(x)}{\sqrt{n_{\text{total}}}}. \quad (30a)$$

EXAMPLE 4: One-way ANOVA

Plasma Creatinine (*P-Creatinine*; amount-of-substance concentration [mmol/L]) was measured in the same control material, five times in each of five runs. Estimate the combined uncertainty appropriate to the next single measurement of this control material.

The 25 measurement quantity values, {*P-Creatinine*}, and one-way ANOVA results are presented in Table 2.

^b When the numbers of data are not the same, ie, the dataset is “unbalanced,” n_0 is

$$n_0 = \frac{N^2 - \sum_{i=1}^m (n_i)^2}{N \times (m - 1)} = \bar{n} - \frac{s_n^2}{N},$$

where m is the number of groups, N is the total number of observations, n_j is the number of data values in the j^{th} group, $\bar{n}$ is the arithmetic mean of the number of results in each run, and s_n the SD of the n_j values. The value of n_0 will always be between the smallest and largest of the n_j . If the difference between the number of observations in each group is small, $\bar{n}$ is generally an adequate approximation.

Table 2. Results of Five Repeated Measurements (Replicates) in Five Runs and the Output Generated With the ANOVA Single-Factor Analysis Method Provided in a Spreadsheet Program

Replicates	Data				
	Run 1	Run 2	Run 3	Run 4	Run 5
1	140	138	143	143	142
2	140	139	144	143	143
3	140	138	144	142	141
4	141	137	145	143	142
5	140	139	143	142	143

Groups	Summary			
	Count	Sum	Average	Variance
Run 1	5	701	140.20	0.20
Run 2	5	691	138.20	0.70
Run 3	5	719	143.80	0.70
Run 4	5	713	142.60	0.30
Run 5	5	711	142.20	0.70

Source of Variation	ANOVA					
	SS	df	MS	F	P-value	F crit
Between run	97.6	4	24.4	46.9	0.0	2.9
Within run	10.4	20	0.52			
Total	108.0	24				

The “between-run” MS is $MS_{btw} = 24.4$, the “within-run” MS is $MS_{wth} = 0.52$, and n_0 is 5.

From Equation 27, the value for $s_{wth} = \sqrt{0.52} = 0.72$ mmol/L;

from Equation 28, $s_{btw} = \sqrt{\text{MAX}\left(0, \frac{24.4 - 0.52}{5}\right)} = \sqrt{4.78} = 2.19$ mmol/L; and

from Equation 29, $u_c(P\text{-Creatinine}) = \sqrt{2.19^2 + 0.72^2} = \sqrt{5.30} = 2.30$ mmol/L.

NOTE: This value of $u_c(P\text{-Creatinine})$ estimates the uncertainty for single measurements of this particular control material measured under the same conditions (ie, same reagent lot).

For these data, the simple SD of the 25 data measurements is 2.12 mmol/L and provides a similar estimate for $u_c(P\text{-Creatinine})$. However, the SD calculated directly from an entire dataset will increasingly underestimate $u_c(P\text{-Creatinine})$ as differences between the runs increase.

A worked example of estimating the uncertainty from IQC is included in Appendix B.

7.4 Uncertainty Profiles

For many measurements in clinical laboratory medicine, the uncertainty varies as a function of the measured value. 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, $u(x)$. In some cases, it is reasonable to consider both a constant and a relative contribution to the uncertainty because the SD of

repeated measurements often tends to be fairly constant at low values, whereas the %CV tends to be fairly constant at high concentrations.

An uncertainty profile of a measurement describes the variation of the uncertainty at different concentrations in the measuring interval. The uncertainty profile is a characteristic of a specific measurement procedure. Ideally, uncertainty profiles should illustrate the uncertainty across the entire measuring interval. They are often displayed as a curve relating some measure of imprecision (eg, repeatability) on the vertical axis to quantity values (eg, concentration) on the horizontal axis. Figure 3 illustrates the uncertainty profile for P-Troponin I concentration measurements estimated from duplicate measurements taken over a period of five days. The uncertainty expressed in absolute terms is almost constant at the low concentrations, whereas the relative uncertainty becomes constant at higher concentrations.

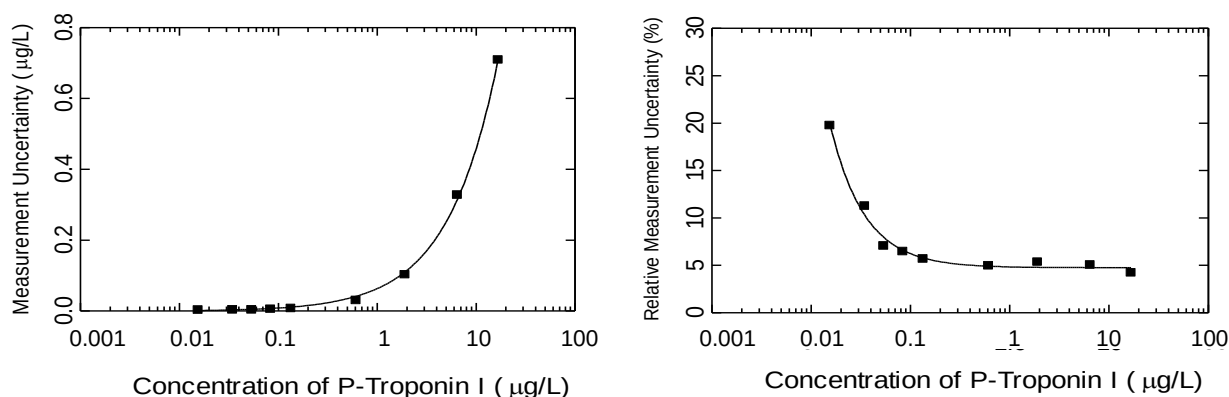


Figure 3. Uncertainty Profiles of P-Troponin I Concentration Measurements. The left panel shows the absolute and the right the relative uncertainty.

Verification of a measurement procedure should include establishing an uncertainty profile. Information from the uncertainty profile may be used in the clinical setting to determine the minimal difference (MD) between a result and a clinical decision value (reference value) that can be measured with a stated level of confidence (see Section 9.3). Software is available that can greatly simplify profile estimation.³⁴

7.5 Use of Results From Interlaboratory Comparisons

Interlaboratory comparison studies are known by many names, including “proficiency tests,” “external quality assessment schedules,” “collaborative reference programs,” “collaborative analytical studies,” “multicenter studies,” “ring trials,” and “round robin exercises.”^{35,36} In addition to monitoring the performance of an individual laboratory, these studies may characterize materials, analytical procedures, and the state of the art within a defined measurement community. Thus, the studies vary widely in their primary goals and there is probably no single design that meets them all.³⁷ Unless specifically designed for the task, these studies are of very limited value for characterizing the measurement uncertainty characteristics of a measurement procedure within a particular laboratory.^{38,39} However, interlaboratory comparison programs may be used to *verify claims* of measurement uncertainty.⁴⁰ For example, if a proficiency testing program evaluates performance using a commutable material with a metrologically traceable value, rather than a consensus value, the difference between a laboratory’s result and the reference value should be less than the combined expanded uncertainties claimed by the laboratory and stated for the value of the reference material. Study designs involving several well-characterized, traceable, and commutable test materials for each measurement procedure and measurand may be used to characterize measurement uncertainty for individual processes.⁴¹ A series of related individual studies conducted over a period of time can be used to characterize long-term performance.⁴² The evaluation of data from such studies is beyond the scope of this document.

7.6 Unsatisfactory Results

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 subprocesses 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.

8 Bias Assessment

8.1 Bias

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.

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. Therefore, additional ways to assess bias, for example, comparing results of measurements of patient samples by different methods, instruments, or laboratories, are used. Methods for assessing bias are discussed in CLSI documents EP07,⁴³ EP09,¹⁸ and EP15.²⁰

Any uncertainty model needs to accommodate both the bias formally linked to the traceability of the calibrator to one or more reference materials of a higher order and to influences of other input quantities, eg, the matrix of the sample and any interfering substances.⁴⁴ Pre- and postmeasurement uncertainties may also need to be considered (see Section 6.5).

8.2 Bias Correction

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; see Magnusson and Ellison²⁵ for a comprehensive review and discussion of consequences.

8.3 Estimating the Uncertainty of the Bias Correction

Even when a bias is determined to be insignificant, the uncertainty in that determination should be included in the calculation of uncertainty of the result. The uncertainty of the bias correction can be assessed by either Type A or Type B procedures. In Examples 5 and 6, two common approaches are described (see CLSI document EP15²⁰), which illustrates the Type A procedure.

8.3.1 Comparison of Methods

When results of a test method are compared with results of a reference or a conventional method (see CLSI document EP15²⁰), a regression function can be estimated (see CLSI document EP09¹⁸). This function, $X_{\text{test}} = f(X_{\text{reference}})$, can be used to reassign either a value of the calibrator or the test method's results. The expected function for two validated methods is a straight line having unit slope and zero intercept. In any case, such functions are estimated with uncertainty and may be valid only for the sample populations and concentration intervals from which they were derived.

EXAMPLE 5: Uncertainty in bias estimation from a comparison between results of measurements (the assumptions and values used in this example have been simplified for illustrative purposes)

In a bias estimation experiment, the concentration of X in a suitably large number, n , of patient samples was measured by a reference method and by a test method. The concentrations in these samples, by the reference method, ranged from 22 to 52 units/L. The test method measurement imprecision, $s(x_{\text{test}})$, was determined to be constant over this entire interval.

The bias (b_i) was estimated as the difference between the result provided by the test method and that of the reference method, $b_i = x_{i,\text{test}} - x_{\text{reference},i}$.

From Equation 1, the estimate of the bias is $\bar{b} = \sum_{i=1}^n b_i / n$ units/L.

From Equation 2, the SD of the differences is $s(b) = \sqrt{\sum_{i=1}^n (b_i - \bar{b})^2 / (n-1)}$ units/L.

From Equation 5, the SD of the estimated bias is $s(\bar{b}) = s(b) / \sqrt{n}$ units/L.

From Equation 10, the combined uncertainty of a test method result is $u_c = \sqrt{s^2(x_{\text{test}}) + s(\bar{b})^2}$ units/L.

Assume that $n = 144$, $s(b) = 1.2$ units/L, and $s(x_{\text{test}}) = 0.71$ units/L. Then $s(\bar{b}) = 1.2 / \sqrt{144} = 0.10$ units/L and $u_c = \sqrt{0.71^2 + 0.10^2} = 0.72$ units/L.

If $\bar{b}$ is between about -2×0.10 units/L and 2×0.10 units/L, results from the test method may not require bias correction but the uncertainty of the reported uncorrected results should include the uncertainty of the bias determination and may thus be slightly larger than the method imprecision alone. Should $\bar{b}$ be outside this interval, then the test method is biased relative to the reference method and a recalibration considered. If the test method is recalibrated to eliminate the observed bias then the relative combined uncertainty is expressed in relation to the bias-corrected result.

Now assume the same quantities, except let $n = 16$. Then $s(\bar{b}) = 1.2 / \sqrt{16} = 0.30$ units/L, $u_c = \sqrt{0.71^2 + 0.30^2} = 0.77$ units/L, and the 95% level of confidence interval about zero bias is -0.60 units/L to 0.60 units/L. The number of samples needed to detect significant bias depends on how “significance” is defined: does a result differing by ± 0.2 units/L have clinical significance, or by ± 0.6

units/L? Note, however, that the number of samples needed to adequately inform the bias correction component of the overall uncertainty is very dependent on the magnitudes of the other components.

8.3.2 Evaluation of a Natural Matrix Certified Reference Material

When available, natural matrix CRMs are often evaluated as part of a laboratory's method verification protocol. These materials are designed to have properties as similar as possible to those expected for patient samples and can serve to verify that the materials used to calibrate a method are suitably commutable. Natural matrix CRMs may also be used during the evaluation of QC materials to help resolve whether observed changes are related to drift in the measurement method or to QC material degradation.

EXAMPLE 6a: Uncertainty in bias estimation using CRMs

To access the bias of a measurement procedure, a laboratorian repeatedly measured the concentration of a particular measurand, X , in a commutable CRM having a certified concentration of 6.3 ± 0.1 units/L ($k = 2$). Duplicate measurements were made in six different runs^c on independently prepared aliquots of the CRM material. The within-run duplicate measurements were made under repeatability conditions. There were no intentional changes in these conditions between runs, but there may have been small unintentional changes in, for example, reagents and environmental factors. Table 3 lists the 12 measurement values, x_{ij} , where i indexes the runs and j indexes the replicates.

Table 3. Measured Quantity Values for Component X in a CRM

Measurement Runs	Replicate 1	Replicate 2
1	6.0	6.1
2	6.1	6.3
3	5.9	6.0
4	6.0	5.9
5	5.8	6.1
6	6.0	6.3

The mean, $\bar{x}$, of these 12 measurements is 6.04 units/L. From a one-way ANOVA, the $MS_{\text{with}} = 0.02083$ and between-run mean square is $MS_{\text{btw}} = 0.02483$. By Equation 30, the standard uncertainty of the mean is

$$u_c(\bar{x}) = \sqrt{\frac{MS_{\text{btw}}}{n_{\text{total}}}} = \sqrt{\frac{0.02483}{12}} = 0.045 \text{ units/L.}$$

The certified concentration of X in the commutable CRM material, $x_{\text{CRM}} \pm U(x_{\text{CRM}})$, is 6.3 ± 0.1 units/L, where $U(x_{\text{CRM}})$ is an expanded uncertainty at the 95% level of confidence. Following typical metrological practice, the standard uncertainty of the certified value, $u(x_{\text{CRM}})$, is $U(x_{\text{CRM}})/2 = 0.05$ units/L. The bias between the measured mean and the certified value of X is thus

$$b = \bar{x} - x_{\text{CRM}} = 6.04 - 6.3 = -0.26 \text{ units/L,}$$

and the combined standard uncertainty of b is

$$u_c(b) = \sqrt{(u_c(\bar{x}))^2 + u(x_{\text{CRM}})^2} = \sqrt{(0.045)^2 + (0.05)^2} = 0.068 \text{ units/L.}$$

^c More measurements are desirable; but due to the limited availability of CRMs, six observations are considered practical.

Because the observed bias, $b = -0.26$ units/L, is not covered by the expanded uncertainty interval,

$$\pm 2 \times u_c(b) = \pm 2 \times 0.068 = -0.14 \text{ units/L to } 0.14 \text{ units/L,}$$

the bias cannot be asserted to be zero and consideration should be given to recalibrating the measurement method, either directly, using calibration materials with better commutability properties, or by correcting for the observed bias.

EXAMPLE 6b: Uncertainty of a bias-corrected future result

After having determined the bias of the measurement procedure and establishing that calibration materials were the best available, the laboratorian wishes to estimate the uncertainty appropriate for future bias-corrected measurements. The literature-claimed 95% long-term single laboratory imprecision for the measurement procedure as “typically” implemented is $\pm 7\%$ of the measurement result:

$$U(x) = \frac{7}{100} \times x = 0.07 \times x \text{ units/L.}$$

Again, following metrological practice, the standard uncertainty expected for a single future measurement made in a typical laboratory is thus

$$u_c(x) = \frac{U(x)}{2} \times x = \frac{0.07}{2} \times x = 0.035 \times x \text{ units/L.}$$

The expected uncertainty for the future measurement after bias correction, $x - b$, combines the expected uncertainty of the measurement procedure with the estimated uncertainty of the bias correction:

$$u_c(x - b) = \sqrt{u_c^2(x) + u_c^2(b)} = \sqrt{(0.035 \times x)^2 + 0.068^2} \text{ units/L.}$$

If the 6.3 units/L CRM was to be measured again, the expected result of the measurement would be the 6.04 units/L mean value determined previously. The bias-corrected result would be

$$6.04 - (-0.26) = 6.04 + 0.26 = 6.3 \text{ units/L,}$$

with an expected uncertainty of

$$\mu_c(6.04 - (-0.26)) = \sqrt{(0.035 \times 6.04)^2 + 0.068^2} = \sqrt{0.0447 + 0.0046} = 0.22 \text{ units/L.}$$

Alternatively, the ANOVA of the measurement values in Table 3 could be used to estimate the imprecision of the measurement process in the laboratorian's hands. Recalling that $MS_{\text{wth}} = 0.02083$ and $MS_{\text{btw}} = 0.02483$, by Equations 27 and 28,

$$s_{\text{wth}} = \sqrt{MS_{\text{wth}}} = \sqrt{0.02083} = 0.144 \text{ units/L,}$$

and

$$s_{\text{btw}} = \sqrt{\text{MAX}\left(0, \frac{MS_{\text{btw}} - MS_{\text{wth}}}{n_0}\right)} = \sqrt{\frac{0.02483 - 0.02083}{2}} = \sqrt{0.00400} = 0.045 \text{ units/L.}$$

By Equation 29, the combined uncertainty for a future measured value of 6.04 units/L is

$$u_c(6.04) = \sqrt{s_{\text{wth}}^2 + s_{\text{btw}}^2} = \sqrt{0.144^2 + 0.045^2} = 0.151 \text{ units/L.}$$

By converting this estimate into an expanded uncertainty and expressing it in percent relative form,

$$\frac{2 \times u_c(x)}{x} \times 100 = \frac{2 \times 0.151}{6.04} \times 100 = 5.0 \%,$$

it appears that the laboratorian's implementation of the measurement procedure is somewhat more precise than the literature claim. Using the directly estimated $u_c(6.04)$, the expected uncertainty for the laboratorian's single bias-corrected measurement of the 6.3 units/L CRM would be

$$\mu_c(6.04 - (-0.26)) = \sqrt{0.151^2 + 0.068^2} = 0.165 \text{ units/L.}$$

9 Uses of Uncertainty Estimates

9.1 Reporting Measurement Results and Their Uncertainties

Measurement results cannot be compared with other results or with reference values unless information concerning their reliability is available to those performing measurements and those receiving results (clinical users). Although in practical work, clinical experience may suffice, medical laboratories may wish to make measurement uncertainties available to clinical users.

For electronic databases, the following information is recommended for each measurement:

- Measurement quantity value, x
- Combined standard uncertainty of x , $u_c(x)$
- The coverage factor (k) and/or the expanded uncertainty, $U(x) = k \times u_c(x)$
- The units of x
- Whether the uncertainty should be reported in the units of measurement or as a percentage of the measurement

When presenting the measurement result with its uncertainty to a user, report the:

- x
- Units of the measurement
- $U(x)$ or $\%U(x)$
- Units of the uncertainty, ie, either the units of measurement or percent
- Coverage factor k used to calculate $U(x) = k \times u_c(x)$ or level of confidence, eg, 95%

Several formats are commonly used for expressing the result and its uncertainty. The GUM¹ recommends the complete form:

“S-Creatinine; substance concentration = $(50 \pm 1) \mu\text{mol/L}$, where the number following the symbol $\pm$ is the expanded uncertainty $U = k \times u_c$, with U determined from (a combined standard uncertainty) $u_c = 1 \mu\text{mol/L}$ and (a coverage factor) $k = 2$ and defines an interval estimated to have a level of confidence of 95 percent.”

In practice, “{S-Creatinine} = (50 ±1) μmol/L, $k = 2$ ” is as informative and rather more compact.

9.2 Number of Significant Digits

The numerical value of a measurement (x); its standard uncertainty, $u_c(x)$; or its expanded uncertainty $U(x)$, should not be given with an excessive number of digits. It usually suffices to quote $u_c(x)$ and $U(x)$ to, at most, two significant digits. 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.

9.3 Clinical Use of Measurement Uncertainty Estimates

Results of measurements are used in different situations in which the uncertainty plays a role. The uncertainty should be appropriate for the concentration interval and the uncertainty profile of the measurement procedure should be considered (see Section 7.4). The clinical value and use of the uncertainty will increase as data accumulate and the laboratory information systems become capable of comparing new results with previous results, ie, “delta checks.”

9.3.1 Patient Monitoring, Same Uncertainty

Monitoring means that a measurement is repeated on a different sample collected from the same patient at a different time, and the two results, x_1 and x_2 , are assessed for clinically significant changes. If the two samples are analyzed by the same laboratory using the same measurement system, it can be reasonably assumed that the uncertainty of both results will be the same, $u(x_1) = u(x_2)$. Although both results are usually considered best estimates, if both were to be repeated, then the new results could fall on either side of the originals, with a probability distribution described by the SD of the measuring system. For this reason, a two-tailed probability test is used, typically using $k = 2$ for an approximate 95% level of confidence. The following examples will consider only the uncertainties of the measurements themselves. In the clinical situation, other influence factors need to be considered, eg, pre- and postmeasurement uncertainties, the time between repeated measurements, and possible covariances or correlations between results.

The reference change value (RCV) is the minimum difference of a measurement from a reference value that is considered as distinguishable from measurement uncertainty. Thus, $RCV > k \times |x_1 - x_2|$ is required for there to be a probability that the two measurements differ. (Use of $k = 2$ provides about a 95% level of confidence in the decision.)

$$RCV > U(|x_1 - x_2|) = k \times \sqrt{u^2(x_1) + u^2(x_2)} = 2 \times \sqrt{2} \times u(x_1) = 2.83 \times u(x_1)$$

Rounding the factor 2.83 to 3 gives the usual “rule of thumb” that the absolute value of the difference between two successive measurements must be greater than three times the measurement uncertainty to be considered different.

EXAMPLE 7: Two measurements having the same uncertainty

The S-Sodium amount-of-substance concentration was found to be 137 mmol/L with a standard measurement uncertainty of 0.5%. A new sample was measured a few hours later. The MD that would be considered significant is

$$MD > 2.83 \times \frac{0.5 \times 137}{100} = 1.9 \text{ mmol/L,}$$

or, using the “rule of thumb,”

$$MD > 3 \times \frac{0.5 \times 137}{100} = 2.1 \text{ mmol/L.}$$

Therefore, if the two results differ by 2 mmol/L or more, the difference is statistically significant at about a 95% level of confidence and the two results are analytically distinguishable.

9.3.2 Patient Monitoring, Different Uncertainties

If the sample is sent to different laboratories or there is reason to assume that the uncertainty is different between the measurement occasions, both uncertainties must be considered. In all cases, additional sources of uncertainty, eg, preanalytical (preexamination) effects, should be considered and, if necessary, combined with one or both of the measurement uncertainties (see Section 6.5).

EXAMPLE 8: Two measurements with different uncertainties

The S-Sodium amount-of-substance concentration was found to be 137 mmol/L measured in the emergency room with a measurement uncertainty of 1%. It was later measured by the laboratory with a measurement uncertainty of 0.5%. The minimum significant difference between the two values that could be distinguished from measurement uncertainty is

$$\begin{aligned} MD &> k \times \sqrt{u^2(x_1) + u^2(x_2)} \\ &= 2 \times \sqrt{\left(\frac{1 \times 137}{100}\right)^2 + \left(\frac{0.5 \times 137}{100}\right)^2} = 2 \times \sqrt{1.88 + 0.47} = 3.0 \text{ mmol/L.} \end{aligned}$$

9.3.3 Clinical Diagnosis Comparison of a Result to Reference Intervals or Decision Limits

A measurement result, x , is compared with a biological reference interval, x_{low} to x_{high} , or clinical decision limit (x_{limit}). If x lies outside the reference interval or above (or below) a decision limit (depending on the nature of the limit), the probability for disease or risk is believed to be larger than if x is within the interval or does not exceed the limit. Reference intervals and decision limits are determined by a variety of ways, but once defined, their values are considered to have no associated uncertainty, $u(x_{\text{low}}) = u(x_{\text{high}}) = u(x_{\text{limit}}) = 0$.

A patient result (x) is considered to deviate from a clinical decision limit if it differs from the limit by an amount that exceeds a given MD. MD is defined such that the probability of exceeding it is small when the true value of the quantity is not above or below the limit. For a reference interval, the patient result x is considered to lie outside the interval if either $(x_{\text{low}} - x)$ or $(x - x_{\text{high}})$ exceeds the MD. MD is defined to be the expanded uncertainty $k \times u(x)$, where coverage factor k specifies the desired level of confidence. Because only values above or below a limit give cause for concern, the comparison is one-sided, and k is defined accordingly. For an approximate one-sided 95% level of confidence, $k = 1.65$, assuming a normal distribution. (This contrasts with $k = 2$ for two-sided 95% level of confidence.)

EXAMPLE 9: Comparison of a value with a decision limit

The serum cholesterol (S-Cholesterol) amount of substance concentration was found to be 5.5 mmol/L. The standard measurement uncertainty was 3%. The MD for a result, x , to indicate a concentration above the upper limit of the reference interval, x_{high} , with a probability of 95% is

$$MD > x - x_{\text{high}} = 1.65 \times \frac{3}{100} \times 5.5 = 0.27 \text{ mmol/L.}$$

Therefore, for a limit of 5 mmol/L, any result above 5.3 mmol/L would be significantly above the limit.

NOTE: MD is computed assuming the measurement error is normally distributed.

9.3.4 Uncertainty of Calculated Quantities

In certain cases, additional clinical value can be achieved by combining results of different markers in an algorithm. This can be based on:

- Physiological principles (eg, creatinine clearance, erythrocyte mean corpuscular volume)
- Population studies (eg, estimated glomerular filtration rate, estimated average glucose [eAG])

Because the measurement uncertainty concept expresses all uncertainty in an identical manner, it is possible to combine the uncertainties of the input quantities of such algorithms to estimate a combined standard uncertainty.

EXAMPLE 10: Uncertainty of calculated patient system (Pt) Creatinine clearance

The Pt Creatinine clearance (Cl_{cr}) volume rate is calculated as

$$Cl_{cr} = \frac{1}{\{S-Crea\}} \times \frac{\{U-Vol\} \times \{U-Crea\}}{Time}.$$

where $\{U-Volume\}$ is the urine volume in milliliters collected during $Time$ minutes with a concentration of $\{U-Creatinine\}$ in mmol/L, and $\{S-Creatinine\}$ is the serum concentration of creatinine in $\mu\text{mol/L}$. Suppose $\{U-Creatinine\}$ is measured with a combined uncertainty of 3%, $\{S-Creatinine\}$ with 5%, the standard uncertainty of the time of collection is 15 minutes, and the standard uncertainty of the measured volume is 1.5%. The voided urine volume (1500 mL) could be up to 200 mL larger than that collected and measured.

Assuming that the maximum underestimation of the urine volume (200 mL) defines a rectangular distribution centered at the half-interval, $\{U-Volume_{prea}\} = 100$ mL, and the best estimate, $\{U-Volume\} = 1500 + 200/2 = 1600$ mL. The standard uncertainty of this preanalytical (preexamination) volume is

$$u(U-Vol_{prea}) = \frac{200}{2 \times \sqrt{3}} = 57.7 \text{ mL}.$$

See Appendix A for information on the estimation of the standard uncertainty of a rectangular distribution.

The complete measurement function is then,

$$Cl_{cr} = \frac{1}{\{S-Crea\}} \times \frac{(\{U-Vol\} + \{U-Vol_{prea}\}) \times \{U-Crea\}}{Time}.$$

As witnessed with Example 3, a pencil-and-paper evaluation of $u(Cl_{cr})$ for this mixed-operation function is somewhat involved. A better option is to use a computer program, eg, the Kragten template^{26,45,46} or Monte Carlo methods,⁴⁷ for all but the simplest uncertainty calculations. Certain limitations apply to some methods, eg, the usual Kragten approximation requires independent input quantities and cannot handle complex functions such as exponential functions, eg, those found in the algorithm for the “estimated glomerular filtration rate.”

Figure 4 displays a Kragten analysis for this measurement function with the specified input quantities and uncertainties. With these assumptions, the combined relative uncertainty is 6.9% and the major source of the uncertainty is the measurement of serum creatinine concentration.

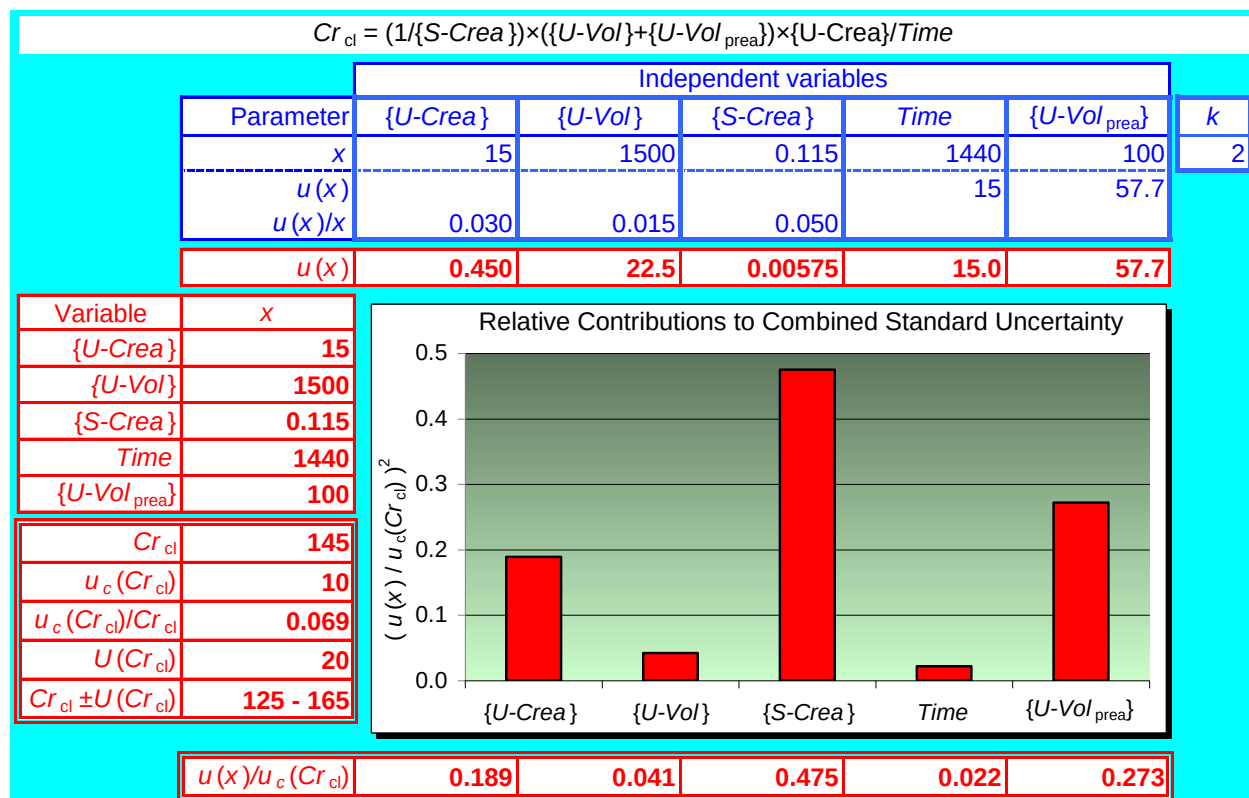


Figure 4. Numerical Approximation of the Combined Uncertainty According to Kragten

However, although tedious, assuming that all of the quantities are independent, the uncertainty is

$$\frac{u(Cl_{cr})}{Cl_{cr}} = \sqrt{\left(\frac{u(S-Crea)}{\{S-Crea\}}\right)^2 + \frac{u^2(U-Vol) + u^2(U-Vol_{prea})}{(\{U-Vol\} + \{U-Vol_{prea}\})^2} + \left(\frac{u(U-Crea)}{\{U-Crea\}}\right)^2 + \left(\frac{u(Time)}{Time}\right)^2},$$

and with the input quantities from Figure 4,

$$\frac{u(Cl_{cr})}{Cl_{cr}} = \sqrt{0.05^2 + \frac{22.5^2 + 57.7^2}{1600^2} + 0.03^2 + \left(\frac{15}{1440}\right)^2} = 0.071.$$

The difference between the estimates (0.071 vs 0.069) may be attributable to the approximations used in the Kragten analysis.

EXAMPLE 11: Uncertainty for a prediction equation derived from a linear regression

An algorithm for predicting eAG from measurements of glycated hemoglobin (A_{1C}) was recently published⁴⁸ that, with additional information provided by the authors, enables estimation of $u(eAG)$ for a given $A_{1C} \pm u(A_{1C})$ measurement. The prediction equation is

$$eAG = \alpha + \beta \times A_{1C} + \varepsilon, \quad (31)$$

where α and β are the intercept and slope estimated by linear regression of A_{1C} on average glucose (AG) measurements and ε represents the normally distributed random error between the predicted and “true” AG values, $eAG - AG$. By definition, the expected value of ε for any given A_{1C} measurement is zero but with an expected uncertainty of $u(\varepsilon)$.

Applying Equation 10, the expected combined standard uncertainty for a future eAG predicted from an A_{1C} measurement is

$$u_c(eAG) = \sqrt{u^2(\alpha) + u^2(\beta \times A_{1C}) + u^2(\varepsilon) + 2 \times (\text{cov}(\alpha, \beta \times A_{1C}) + \text{cov}(\alpha, \varepsilon) + \text{cov}(\beta \times A_{1C}, \varepsilon))},$$

where $u(\alpha)$ is the estimated uncertainty on the intercept, $u(\beta \times A_{1C})$ is the uncertainty of the product of the slope and a measured A_{1C} value, and $\text{cov}(.,.)$ denotes the covariance between two terms. For any new measurement of A_{1C} , the specific value of ε is not related to the parameters estimated in the regression and all covariance terms involving ε are zero. For any fixed value of A_{1C} , $\text{cov}(\alpha, \beta \times A_{1C})$ is equal to $A_{1C} \times \text{cov}(\alpha, \beta)$. However, because α and β were simultaneously estimated from a given set of data, these values are correlated and $\text{cov}(\alpha, \beta)$ cannot be assumed to be zero. Although the relationship is not at all obvious, for this linear model⁴⁹:

$$\text{cov}(\alpha, \beta) = -\overline{A_{1C}} \times u(\beta),$$

where $\overline{A_{1C}}$ is the average of the A_{1C} values used to define the regression parameters.

Now applying Equation 11a (see Section 3.6.9.3) to expand the $u(\beta \times A_{1C})$ term,

$$u(\beta \times A_{1C}) = \beta \times A_{1C} \sqrt{\left(\frac{u(\beta)}{\beta}\right)^2 + \left(\frac{u(A_{1C})}{A_{1C}}\right)^2 + 2 \times \frac{\text{cov}(\beta, A_{1C})}{(\beta \times A_{1C})^2}},$$

where $u(\beta)$ is the estimated uncertainty of the slope parameters and $u(A_{1C})$ is the standard uncertainty of the A_{1C} measurement. For any fixed value of A_{1C} , $\text{cov}(\beta, A_{1C})$ is equal to zero.

Consolidating and combining the individual terms,

$$u(eAG) = \sqrt{u^2(\alpha) + (A_{1C} \times u(\beta))^2 + (\beta \times u(A_{1C}))^2 - 2 \times A_{1C} \times \overline{A_{1C}} \times u(\beta) + u^2(\varepsilon)}. \quad (32)$$

Using the conventional coverage factor $k = 2$, the approximate 95% level of confidence expanded uncertainty of the predicted value is

$$U(eAG) = 2 \times u(eAG). \quad (33)$$

Table 4 lists numerical values for the various terms. Note that $u(\varepsilon)$ is not constant for all A_{1C} but increases proportionally as A_{1C} increases. Similarly, although the expected value of $u(A_{1C})$ for a given A_{1C} will differ by measurement method and laboratory instrumentation, $0.05 \times A_{1C}$ (a %CV of 5%) was set as the targeted upper bound during the development of one commercial system.⁵⁰

Table 4. Parameters and Values for eAG From Measurements of A_{1C}

Parameter	Symbol	Value	Units	Source
Intercept	α	-46.6	mg/dL	Table 2 in Nathan et al. ⁴⁸
Standard uncertainty of α	$u(\alpha)$	3.8	mg/dL	Estimated Type B
Slope	β	28.7	mg/dL/%	Table 2 in Nathan et al. ⁴⁸
Standard uncertainty of β	$u(\beta)$	0.6	mg/dL/%	Estimated Type B
Expected prediction bias	ε	0	mg/dL	Definition
Expected prediction uncertainty	$u(\varepsilon)$	$2.21 \times A_{1C}$	mg/dL	Table 2 in Nathan et al. ⁴⁸
Mean A_{1C} of regression data	$\overline{A_{1C}}$	6.8	%	Table 1 in Nathan et al. ⁴⁸
Measurement value	A_{1C}	2 to 15	%	Literature
Standard uncertainty of A_{1C}	$u(A_{1C})$	Laboratory specific	%	
Predicted value	eAG	Equation 31	mg/dL	
Standard uncertainty of eAG	$u(eAG)$	Equation 32	mg/dL	
Expanded uncertainty of eAG	$U(eAG)$	Equation 33	mg/dL	

Figure 5 displays the summary data listed in the article by Nathan and associates⁴⁸ and the modeled relationship between eAG and A_{1C} . Overlaid on these data and relationships, Figure 5 displays the $eAG \pm U(eAG)$ intervals calculated with Equations 31 and 32 for three values of $u(A_{1C})$: 0%, $0.02 \times A_{1C}\%$ (ie, 2%), and $0.05 \times A_{1C}\%$ (ie, 5%). Within the interval of the A_{1C} values reported in the article,⁴⁸ the calculated 95% intervals for $u(A_{1C})$ of 0% and $0.02 \times A_{1C}\%$ agree very well with the empirical 95% intervals. For $u(A_{1C}) = 0.05 \times A_{1C}$, the predicted 95% interval is outside the empirical error bars.

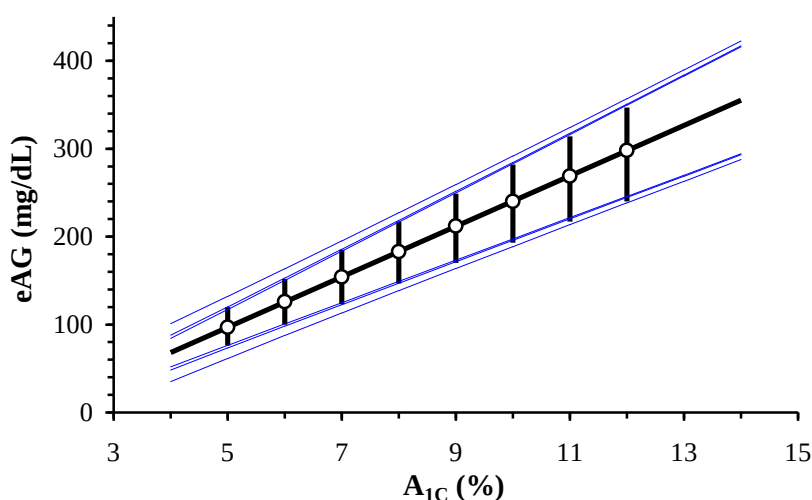


Figure 5. Uncertainty Intervals for the Estimation of AG From Measurements of A_{1C} With Three Assumed Values of $u(A_{1C})$. The dot-and-bar symbols denote the summary data and empirical 95% confidence intervals in the article by Nathan and colleagues.⁴⁸ The thick black line represents predictions using Equation 31. The three sets of solid blue lines represent intervals calculated from Equation 33 using the parameter values given in Table 4 and, in expanding order from the prediction line, $u(A_{1C})$ values of 0%, $0.02 \times A_{1C}\%$, and $0.05 \times A_{1C}\%$.

To better visualize the impact of A_{1C} measurement uncertainty on the prediction of eAG, Figure 6 displays the uncertainties calculated with Equation 32 in the form of relative percent, $\%u_c(eAG) = 100 \times u_c(eAG)/eAG$, for the three values of $u(A_{1C})$. At 2% relative, the uncertainty of A_{1C} measurement does not significantly increase the uncertainty in the predicted eAG values over most of the analytical range. However, 5% relative A_{1C} measurement uncertainty can more than double the expected uncertainty of the predicted value for very low measured values of A_{1C} .

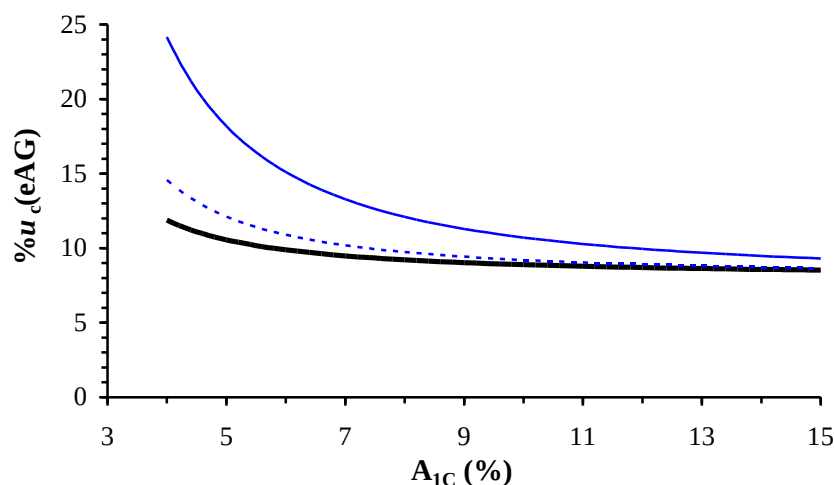


Figure 6. Relative Uncertainty of eAG From Measurements of A_{1C} With Three Assumed Values for $u(A_{1C})$. The thick black line represents the relative uncertainty estimated with Equation 32, assuming that the A_{1C} measurements are exact and have no associated uncertainty. The dashed blue line represents uncertainties estimated assuming a relative A_{1C} measurement uncertainty of 2%; the solid blue line represents 5% relative uncertainty.

10 Summary

The measurement uncertainty can be estimated by different methods. Figure 7 summarizes the bottom-up and the top-down approaches. The bottom-up approach requires that a thorough uncertainty budget is created and that a functional relation between the input variables is defined. The uncertainty of each of the input variables is then assessed by either a Type A or a Type B estimation. The top-down approach estimates the entire process by a Type A or a Type B estimation. The outcome should ideally be the same, but the bottom-up system allows a systematic approach to improvement of the performance. The top-down approach is robust against incomplete models and/or underestimated components in the model.

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.

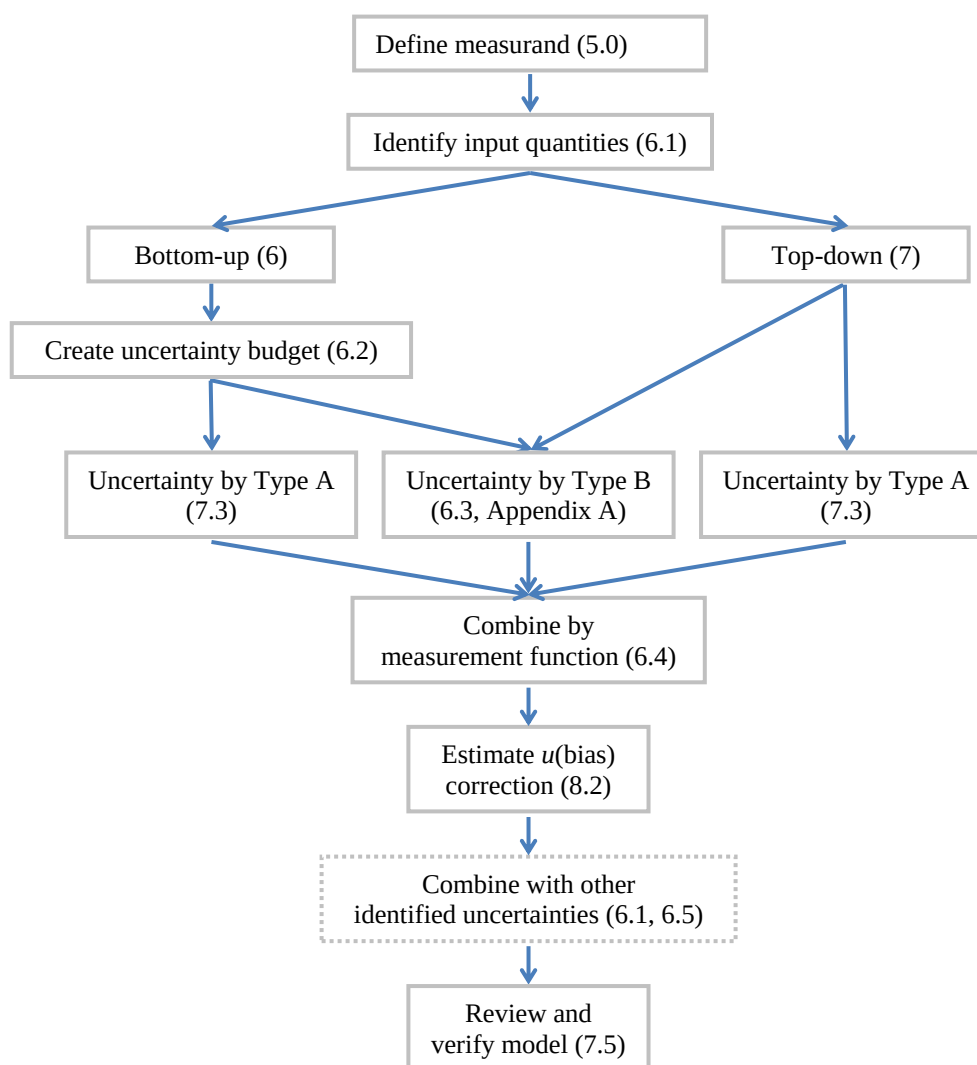


Figure 7. Flow Chart for the Estimation of Measurement Uncertainty Using the Bottom-up or Top-Down Model. Numbers within parentheses refer to sections in the text. The action in the box with the dotted border is conditional to identification and quantification of the sources of uncertainty.

References

- ¹ Bureau International des Poids et Mesures (BIPM). *Evaluation of measurement data – Guide to the expression of uncertainty in measurement* (JCGM 100:2008). <http://www.bipm.org/en/publications/guides/gum.html>. Accessed January 17, 2012.
- ² ISO/TS. *Measurement uncertainty for metrological applications – Repeated measurements and nested experiments*. ISO/TS 21749. Geneva, Switzerland: International Organization for Standardization; 2005.
- ³ ISO. *Guidance for the use of repeatability, reproducibility and trueness estimates in measurement uncertainty estimation*. ISO 21748. Geneva, Switzerland: International Organization for Standardization; 2010.
- ⁴ Bureau International des Poids et Mesures (BIPM). *International Vocabulary of Metrology – Basic and General Concepts and Associated Terms* (VIM, 3rd edition, JCGM 200:2008) and *Corrigendum* (May 2010). <http://www.bipm.org/en/publications/guides/vim.html>. Accessed January 17, 2012.
- ⁵ CLSI. *Laboratory Documents: Development and Control; Approved Guideline—Fifth Edition*. CLSI document GP02-A5. Wayne, PA: Clinical and Laboratory Standards Institute; 2006.
- ⁶ ISO. *Reference materials – Contents of certificates and labels*. ISO Guide 31. Geneva, Switzerland: International Organization for Standardization; 2000.
- ⁷ ISO. *General requirements for the competence of reference material producers*. ISO Guide 34. Geneva, Switzerland: International Organization for Standardization; 2009.
- ⁸ ISO. *Reference materials – General and statistical principles for certification*. ISO Guide 35. Geneva, Switzerland: International Organization for Standardization; 2006.
- ⁹ ISO. *Statistics – Vocabulary and symbols – Part 1: General statistical terms and terms used in probability*. ISO 3534-1. Geneva, Switzerland: International Organization for Standardization; 2006.
- ¹⁰ Thompson M, Wood R. Harmonized guidelines for internal quality control in analytical chemistry laboratories (IUPAC Technical Report). *Pure & Appl Chem*. 1995;67(4):649-666.
- ¹¹ ISO. *Accuracy (trueness and precision) of measurement methods and results – Part 3: Intermediate measures of the precision of a standard measurement method*. ISO 5725-3. Geneva, Switzerland: International Organization for Standardization; 1994.
- ¹² Dybkaer R. An ontology on property for physical, chemical and biological systems. *APMIS Suppl*. 2004;(117):1-210.
- ¹³ ISO. *Medical laboratories – Particular requirements for quality and competence*. ISO 15189. Geneva, Switzerland: International Organization for Standardization; 2007.
- ¹⁴ Dybkaer R. Vocabulary for use in measurement procedures and description of reference materials in laboratory medicine. *Eur J Clin Chem Clin Biochem*. 1997;35(2):141-173.
- ¹⁵ CLSI. *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline—Third Edition*. CLSI document C24-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2006.
- ¹⁶ CLSI/NCCLS. *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition*. CLSI/NCCLS document EP05-A2. Wayne, PA: NCCLS; 2004.
- ¹⁷ CLSI/NCCLS. *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline*. CLSI/NCCLS document EP06-A. Wayne, PA: NCCLS; 2003.
- ¹⁸ CLSI. *Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (Interim Revision)*. CLSI document EP09-A2-IR. Wayne, PA: Clinical and Laboratory Standards Institute; 2010.
- ¹⁹ CLSI. *Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition*. CLSI document EP10-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2006.
- ²⁰ CLSI. *User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition*. CLSI document EP15-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2006.
- ²¹ ISO/IEC. *General requirements for the competence of testing and calibration laboratories*. ISO/IEC 17025. Geneva, Switzerland: International Organization for Standardization; 2005.
- ²² Guthrie WF, Liu H, Rukhin AL, Toman B, Wang JCM, Zhang N. Three statistical paradigms for the assessment and interpretation of measurement uncertainty. In: Pavese F, Forbes AB, eds. *Data Modeling for Metrology and Testing in Measurement Science*. New York, NY: Burkhäuser Boston; 2008:71-114.
- ²³ Petersen PH, Stöckl D, Westgard JO, Sandberg S, Linnet K, Thienpont L. Models for combining random and systematic errors: assumptions and consequences for different models. *Clin Chem Lab Med*. 2001;39(7):589-595.

- ²⁴ CLSI/NCCLS. *Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline*. CLSI/NCCLS document EP21-A. Wayne, PA: NCCLS; 2003.
- ²⁵ Magnusson B, Ellison SL. Treatment of uncorrected measurement bias in uncertainty estimation for chemical measurements. *Anal Bioanal Chem*. 2008;390(1):201-213.
- ²⁶ EURACHEM/CITAC. *Quantifying uncertainty in analytical measurement*. 2nd ed. <http://www.measurementuncertainty.org/mu/QUAM2000-1.pdf>. Accessed January 17, 2012.
- ²⁷ NIST. *Guidelines for evaluating and expressing the uncertainty of NIST measurement results*. Technical Note 1297, 1994 Edition. <http://physics.nist.gov/Pubs/guidelines/TN1297/t1297s.pdf>. Accessed January 17, 2012.
- ²⁸ NIST/SEMATECH *e-Handbook of Statistical Methods: Uncertainty Analysis*. <http://www.itl.nist.gov/div898/handbook/mpc/section5/mpc5.htm>. Accessed January 17, 2012.
- ²⁹ Kristiansen J. Description of a generally applicable model for the evaluation of uncertainty of measurement in clinical chemistry. *Clin Chem Lab Med*. 2001;39(10):920-931.
- ³⁰ Kristiansen J. The Guide to expression of uncertainty in measurement approach for estimating uncertainty: an appraisal. *Clin Chem*. 2003;49(11):1822-1829.
- ³¹ Maroto A, Boqué R, Xavier R. Evaluating uncertainty in routine analysis. *Trends Analyt Chem*. 1999;18(9-10):577-584.
- ³² National Pathology Accreditation Advisory Council (Australia). Requirements for the estimation of measurement uncertainty (2007). [http://www.health.gov.au/internet/main/Publishing.nsf/Content/86A3CE312C612377CA257283007BC92D/\\$File/dhaeou.pdf](http://www.health.gov.au/internet/main/Publishing.nsf/Content/86A3CE312C612377CA257283007BC92D/$File/dhaeou.pdf). Accessed January 17, 2012.
- ³³ ASTM. *Standard Practice for Estimating and Monitoring the Uncertainty of Test Results of a Test Method in a Single Laboratory Using a Control Sample Program*. ASTM E2554-07. West Conshohocken, PA, USA: ASTM International; 2007.
- ³⁴ Sadler WA. Variance Function Program (version 10.0). <http://www.aacb.asn.au/files/File/VFP100.pdf>. Accessed January 17, 2012.
- ³⁵ Libeer JC, Baadenhuijsen H, Fraser CG, et al. Characterization and classification of external quality assessment schemes (EQA) according to objectives such as evaluation of method and participant bias and standard deviation. *Eur J Clin Chem Clin Biochem*. 1996;34(8):665-678.
- ³⁶ Eurachem Proficiency Testing Working Group. Terms and definitions related to proficiency testing. http://www.eurachem.org/wgs/wg_ptmg_files/Reports/Fundamental_Terms_in_PT_Discussion_Paper_Final.pdf. Accessed January 17, 2012.
- ³⁷ Petersen PH. Is it possible to create a perfect external control system? *Scand J Clin Lab Invest*. 1998;58(4):265-268.
- ³⁸ Linko S, Ornemark U, Kessel R, Taylor PD. Evaluation of uncertainty of measurement in routine clinical chemistry – applications to determination of the substance concentration of calcium and glucose in serum. *Clin Chem Lab Med*. 2002;40(4):391-398.
- ³⁹ Thienpont LM, Stöckl D, Friedecký B, Kratochvíla J, Budina M. Trueness verification in European external quality assessment schemes: time to care about the quality of the samples. *Scan J Clin Lab Invest*. 2003;63(3):195-201.
- ⁴⁰ ISO/IEC. *Conformity assessment – General requirements for proficiency testing*. ISO/IEC 17043. Geneva, Switzerland: International Organization for Standardization; 2010.
- ⁴¹ Dimech W, Francis B, Kox J, Roberts G; Serology Uncertainty of Measurement Working Party. Calculating uncertainty of measurement for serology assays by use of precision and bias. *Clin Chem*. 2006;52(3):526-529.
- ⁴² Duewer DL, Kline MC, Sharpless KE, Thomas JB, Gary KT, Sowell AL. Micronutrients Measurement Quality Assurance Program: helping participants use interlaboratory comparison exercise results to improve their long-term measurement performance. *Anal Chem*. 1999;71(9):1870-1878.
- ⁴³ CLSI. *Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition*. CLSI document EP07-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2005.
- ⁴⁴ Eurachem/CITAC. Traceability in chemical measurement: a guide to achieving comparable results in chemical measurement; 2003. http://www.measurementuncertainty.org/pdf/EC_Trace_2003_print.pdf. Accessed January 17, 2012.
- ⁴⁵ Kragten J. A standard scheme for calculating numerically standard deviations and confidence intervals. *Chemometr Intell Lab*. 1995;28(1):89-97.
- ⁴⁶ Kragten J. Tutorial review: calculating standard deviations and confidence intervals with a universally applicable spreadsheet technique. *Analyst*. 1994;119:2161-2165.
- ⁴⁷ JCGM. Evaluation of measurement data — Supplement 1 to the “Guide to the expression of uncertainty in measurement” — Propagation of distributions using a Monte Carlo method. http://www.bipm.org/utils/common/documents/jcgm/JCGM_101_2008_E.pdf. Accessed January 17, 2012.

- ⁴⁸ Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. *Diabetes Care*. 2008;31(8):1473-1478.
- ⁴⁹ Fuller WA. *Measurement Error Models*. Hoboken, New Jersey: Wiley Interscience; 2006.
- ⁵⁰ Holownia P, Bishop E, Newman DJ, John WG, Price CP. Adaptation of latex-enhanced assay for percent glycohemoglobin to a Dade Dimension analyzer. *Clin Chem*. 1997;43(1):76-84.

Additional References

Barwick VJ, Ellison SLR. Estimating measurement uncertainty using a cause and effect and reconciliation approach. Part 2. Measurement uncertainty estimates compared with collaborative trial expectation. *Anal Commun*. 1998;35:377-383.

Barwick VJ, Ellison SLR. Measurement uncertainty: approaches to the evaluation of uncertainties associated with recovery. *Analyst*. 1999;124:981-990.

Ellison SLR, Barwick VJ. Using validation data for ISO measurement uncertainty estimation. Part 1. Principles of an approach using cause and effect analysis. *Analyst*. 1998;123:1387-1392.

EUROLAB. Guide to the evaluation of measurement uncertainty for quantitative test results. EUROLAB Technical Report 1/2006. http://www.demarcheiso17025.com/incertitudes/documentations_incertitudes.html. Accessed January 25, 2012.

EUROLAB. Measurement uncertainty in testing. EUROLAB Technical Report 1/2002. <http://www.eurolab.org>. Accessed January 25, 2012.

EUROLAB. Measurement uncertainty revisited: alternative approaches to uncertainty evaluation. EUROLAB Technical Report 1/2007. http://www.demarcheiso17025.com/incertitudes/documentations_incertitudes.html. Accessed January 25, 2012.

Gleser LJ. Assessing uncertainty in measurement. *Stat Sci*. 1998;13(3):277-290.

ISO. *In vitro diagnostic medical devices – Measurement of quantities in biological samples – Metrological traceability of values assigned to calibrators and control materials*. ISO 17511. Geneva, Switzerland: International Organization for Standardization; 2003.

ISO. *In vitro diagnostic medical devices – Measurement of quantities in biological samples – Metrological traceability of values for catalytic concentration of enzymes assigned calibrators and control materials*. ISO 18153. Geneva, Switzerland: International Organization for Standardization; 2003.

ISO. *In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Requirements for certified reference materials and the content of supporting documentation*. ISO 15194. Geneva, Switzerland: International Organization for Standardization; 2009.

ISO. *In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Requirements for content and presentation of reference measurement procedures*. ISO 15193. Geneva, Switzerland: International Organization for Standardization; 2009.

ISO. *Laboratory medicine – Requirements for reference measurement laboratories*. ISO 15195. Geneva, Switzerland: International Organization for Standardization; 2003.

JCGM. Evaluation of measurement data — An introduction to the “Guide to the expression of uncertainty in measurement” and related documents. http://www.bipm.org/utls/common/documents/jcgm/JCGM_104_2009_E.pdf. Accessed January 17, 2012.

Kenny D, Fraser CG, Hyltoft Petersen P, Kallner A. Consensus agreement: Conference on strategies to set global analytical quality specifications in laboratory medicine. *Scand J Clin Lab Invest*. 1999;59:585.

Krouwer JS. Critique of the Guide to the expression of uncertainty in measurement method of estimating and reporting uncertainty in diagnostic assays. *Clin Chem*. 2003;49(11):1818-1821.

Krouwer JS. Estimating total analytical error and its sources: techniques to improve method evaluation. *Arch Pathol Lab Med*. 1992;116(7):726-731.

Thienpont LM, Van Uytanghe K, De Leenheer AP. Reference measurement systems in clinical chemistry. *Clin Chim Acta*. 2002;323(1-2):73-87.

Thompson M, Ellison SLR. A review of interference effects and their correction in chemical analysis with special reference to uncertainty. *Accred Qual Assur*. 2005;10(3):82-97.

White G. Basics of estimating measurement uncertainty. *Clin Biochem Rev*. 2008;29 Suppl 1:S53-S60.

Appendix A. Transformation of Type B Limit Specifications

By definition, Type B uncertainty evaluations are determined by any “means other than a Type A evaluation of measurement uncertainty.”¹ Typically, Type B evaluations are used when direct repeated measurements are infeasible (eg, the assigned uncertainty on a higher order calibration or verification material), impractical (eg, model uncertainty from a population study), or unnecessary for a particular task (eg, comparing the likely performance of pipettes based on their manufacturers’ specifications). When Type B information is provided in the form of a lower-bound limit (LL) and an upper-bound limit (UL), it is necessary to transform the provided information into a roughly equivalent standard uncertainty (ie, to something that behaves like an SD). LLs and ULs most commonly are used to describe situations in which the expected value is:

- Anywhere between the limits with about equal probability, and there is no chance that the value is outside the limits—the rectangular or uniform distribution
- Anywhere between the limits with the half-width as the most likely value, and there is no chance that the value is outside the limits—the triangular distribution
- A defined probability of being between the limits with the half-width as the most likely, but there is some chance that the value is outside the limits—the gaussian or normal distribution

The rectangular (or uniform) distribution assumes that all effects on the reported value, between LL and UL, are equally likely for the particular source of uncertainty and is a reasonable default model if there is no other information available. If there are indications that values are more likely to be in the center of the interval, then a triangular distribution or a gaussian distribution can be appropriate. If the limits of uncertainty are provided, then the coverage of the stated limits (eg, 95%) can be used to calculate one SD, depending on the distribution assumed. That is, by defining the LL and UL (eg, 90 and 180 units, respectively) and identifying the distribution, a standard uncertainty can be estimated that will have roughly the same coverage properties as those implied by the specification limits. The rectangular distribution is the more conservative (ie, larger uncertainty) of the three distributions. Table A1 presents the formula for converting limit specifications into standard uncertainties for these three distributions.

Table A1. Type B Estimates of Standard Uncertainty

Rectangular Distribution (uniform, bounded)	Triangular Distribution (symmetrical, bounded)	Gaussian Distribution (symmetrical, unbounded)
$u(x) = \frac{UL-LL}{2 \times \sqrt{3}}$	$u(x) = \frac{UL-LL}{2 \times \sqrt{6}}$	$u(x) = \frac{UL-LL}{2 \times \sqrt{9}}$
$u(x) = 26.0 \text{ units}$	$u(x) = 18.4 \text{ units}$	$u(x) = 15.0 \text{ units}$

Example of Weighing Specifications

In a manufacturing environment, the specifications will provide an acceptance interval that uses a measuring device to determine the value. The simplest such device is a balance. When the acceptance interval is broad relative to the uncertainty of the measurement, the uncertainty of the value is driven by the specification.

Consider preparation by weighing a component of a calibrator that has a specification of 156 g ± 1 g. The operator is instructed to stop adding or removing material from the balance once the balance reads a value from 155 to 157 g. A rectangular distribution is assumed because the value can be anywhere in the interval of the specification. From Table A1, the standard uncertainty of the amount weighed is

Appendix A. (Continued)

$$u(156) = \frac{157 - 155}{2 \times \sqrt{3}} = 0.577 \text{ g.}$$

The operator stopped when the balance showed 155.7 g, and thus the nominal quantity value of the calibrator is 155.7 g ± 0.6 g.

The total uncertainty estimate for the weighing has other components, such as linearity and repeatability, that can be neglected so long as they are small relative to the specification. The manufacture's literature states that the balance's readout is expected to be linearly proportional to mass to within ± 0.02 g and repeatable to within the resolution of the digital readout of 0.01 g.

Because the balance must be tared, two weighings are required to determine any given quantity value, *Weight*. Assuming that the linearity and repeatability uncertainty components are best modeled as drawn from triangular $\frac{(UL - LL)}{(2 \times \sqrt{6})}$ and gaussian $\frac{(UL - LL)}{(2 \times \sqrt{9})}$ distributions, respectively, their expected contribution to the overall uncertainty of a given weighing is

$$\begin{aligned} u(\text{Weight}) &= \sqrt{2 \times \left(\frac{0.02 - (-0.02)}{2 \times \sqrt{6}} \right)^2 + 2 \times \left(\frac{0.01 - (-0.01)}{2 \times \sqrt{9}} \right)^2} \\ &= \sqrt{2 \times \left(\left(\frac{0.02}{2.45} \right)^2 + \left(\frac{0.01}{3} \right)^2 \right)} = 0.013 \text{ g.} \end{aligned}$$

However, if the specification is changed to 156.0 g ± 0.1 g and the operator stops when the balance shows 156.07, then the combined uncertainty would be

$$u_c(156.0_{\text{Total}}) = \sqrt{\left(\frac{156.1 - 155.9}{2 \times \sqrt{3}} \right)^2 + 0.013^2} = \sqrt{0.0557^2 + 0.013^2} = 0.059 \text{ g,}$$

and the linearity and repeatability characteristics of the balance begin to have a small influence.

These uses of Type B limit specifications can greatly facilitate the selection of the appropriate procedure and equipment to reach a desired level of performance. However, in applications for clearance or approval of devices by regulatory agencies, when Type A evaluations are practical, they are generally preferred.

In these examples, rounding was not made to better illustrate the point.

These uses of Type B limit specifications can greatly facilitate the selection of the appropriate procedure and equipment to reach a desired level of performance. However, in applications for clearance or approval of devices by regulatory agencies, when Type A evaluations are practical, they are generally preferred.

Appendix A. (Continued)**Reference for Appendix A**

- ¹ Bureau International des Poids et Mesures (BIPM). *International Vocabulary of Metrology – Basic and General Concepts and Associated Terms* (VIM, 3rd edition, JCGM 200:2008) and *Corrigendum* (May 2010). <http://www.bipm.org/en/publications/guides/vim.html>. Accessed January 17, 2012.

Appendix B. Uncertainty Estimates From Routine Quality Control Results

Table B1 presents cholesterol measurement results from daily runs over a six-week period on a single instrument for a single lot of quality control (QC) material. The measurements for Runs 22 to 42 used a different lot of reagents than that used for Runs 1 to 21.

Table B1. Routine Cholesterol Measurement Results for a Single Lot of QC Material

		Reagent Lot A					Reagent Lot B		
Run	Tech	Rep ₁	Rep ₂	Rep ₃	Run	Tech	Rep ₁	Rep ₂	Rep ₃
1	AK	7.9	7.9	8.1	22	AK	7.9	7.9	7.8
2	AK	7.5	7.3	7.6	23	DT	7.6	7.7	7.6
3	DT	7.2	7.2	7.2	24	DT	7.4	7.6	7.4
4	DD	6.6	6.8	6.5	25	AK	7.3	7.2	7.4
5	AK	7.3	7.3	7.3	26	AK	7.7	7.5	7.7
6	AK	7.6	7.5	7.6	27	DT	7.8	7.9	7.7
7	DT	7.5	7.5	7.5	28	DT	8.0	8.0	8.1
8	DT	8.0	8.0	8.0	29	AK	7.9	8.1	7.8
9	AK	7.3	7.3	7.3	30	DT	7.7	7.6	7.7
10	DT	7.8	7.8	7.9	31	DT	7.9	7.7	7.8
11	AK	7.8	7.8	8.0	32	DT	7.5	7.5	7.5
12	AK	7.4	7.5	7.4	33	AK	7.4	7.4	7.6
13	AK	7.5	7.6	7.4	34	DT	7.5	7.5	7.4
14	DT	7.7	7.6	7.7	35	AK	7.7	7.7	7.6
15	AK	7.9	7.9	8.0	36	AK	7.6	7.6	7.8
16	DT	8.0	8.0	8.2	37	AK	7.8	7.9	7.7
17	DT	7.8	7.8	7.7	38	DT	7.8	7.8	7.8
18	DT	7.9	8.1	7.9	39	DT	8.0	7.9	8.0
19	AK	7.5	7.6	7.7	40	AK	7.8	7.7	7.8
20	DT	7.6	7.6	7.8	41	DT	7.9	8.0	7.9
21	DT	7.8	7.6	7.7	42	DT	7.8	7.8	7.9

Consider a situation in which only the “Run” and “Rep₁” data are available, representing a single QC measurement made per run. The mean value for the first 21 results is 7.60 mmol/L with a standard deviation (SD) of 0.33 mmol/L. The mean value for the second 21 results is 7.71 mmol/L with an SD of 0.20 mmol/L. The mean for all 42 results is 7.66 mmol/L with an SD of 0.28 mmol/L. Figure B1 displays the measurement results as a function of Run number, along with lines representing the mean value (solid blue lines) and 95% level of confidence intervals (solid red lines) for each of the two sets of 21 results and the 95% intervals (dashed red lines) for all 42 measurements. Given the relatively large number of independent measurements, use of the coverage factor $k = 2$ is justified and the confidence intervals are calculated as $\text{Mean} \pm 2 \times \text{SD}$.¹

The shift in the mean values and the somewhat different widths of the 95% intervals may be consistent with usual shifts and therefore the small differences can be considered to reflect the increased variability expected with longer-term measurement conditions. The overall mean and SD suggest that the coefficient of variation expressed in percent [%CV]) = $100 \times 0.28/7.66 = 3.6\%$ for an expanded uncertainty of $\%U = 2 \times 3.6 = 7.2\%$.

Appendix B. (Continued)

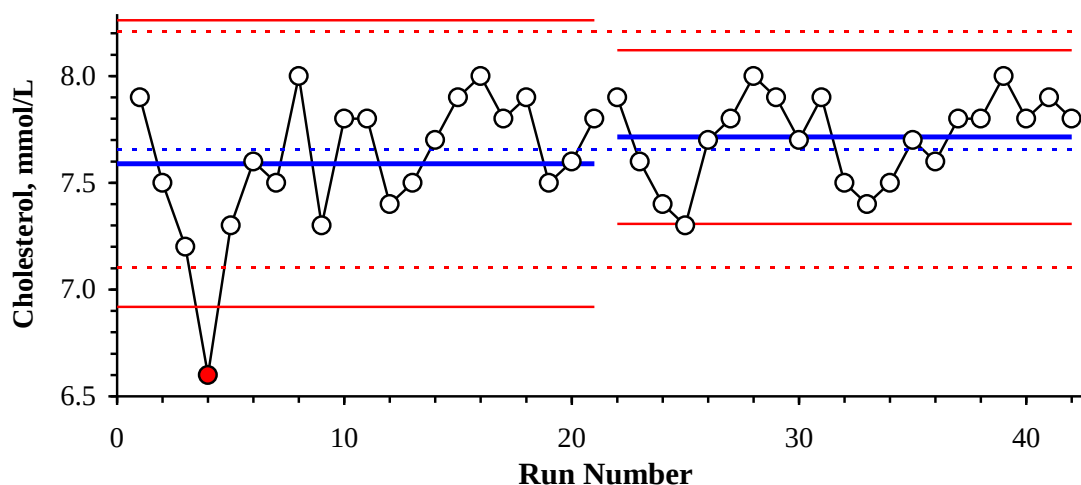


Figure B1. Control Chart for One QC Measurement per Run. Dotted lines refer to the overall average and SD. The solid lines refer to those of the reagent lots A and B.

On closer inspection, the 6.6 mmol/L result produced in Run 4 was excluded as technically suspect, and the mean value for the first 20 valid results is 7.65 mmol/L with an SD of 0.24 mmol/L and the overall mean is 7.68 mmol/L with an SD of 0.22 mmol/L. The overall mean and SD now suggest a %CV of about 2.9% and %U of 5.8%.

Consider now the situation in which “Rep₂” and “Rep₃” results are available in addition to “Run” and “Rep₁,” representing three QC measurements per run. These additional results enable use of analysis of variance (ANOVA) components (see Section 7.3 of this document) to estimate within-run as well as between-run imprecision. Table B2 displays results from a one-way ANOVA for these data, with the technically suspect results for Run 4 removed.

Table B2. ANOVA Results for Three QC Results per Run

Source of Variation	SS	df	MS	F	p-value	F-crit
Between Groups	6.09	40	0.152	21.5	1.24E-29	1.54
Within Groups	0.58	82	0.00707			
Total	6.67	122				

Abbreviations: *df*, degrees of freedom; *MS*, mean square; *SS*, sum of squares.

Following the procedure in Section 7.3 of this document,

$$s_{\text{wth}} = \sqrt{MS_{\text{wth}}} = \sqrt{0.00707} = 0.084 \text{ mmol/L},$$

$$s_{\text{btw}} = \sqrt{\max(0, (MS_{\text{btw}} - MS_{\text{wth}}) / n_0)} = \sqrt{(0.152 - 0.00707) / 3} = \sqrt{0.0483} = 0.220 \text{ mmol/L},$$

$$u_c(x) = \sqrt{0.0483 + 0.00707} = 0.235 \text{ mmol/L and } U = 2 \times u_c = 0.470 \text{ mmol/L}.$$

The grand average of the 123 valid measurements is 7.69 mmol/L. The %CV of the valid measurements is thus $\%U(x) = 100 \times 0.470 / 7.69 = 6.1\%$.

This estimate for %U is slightly larger than the 5.8% from the single results per run scenario because it takes into account the within-run variability.

Appendix B. (Continued)

Quantity value results of two or more control materials having different levels of cholesterol would enable a more complete characterization of the imprecision components of the measurement process. The characterization could be expanded to reflect the performance of several instruments in a laboratory or that of several laboratories.² Measurement bias could be estimated if the control materials have been appropriately value-assigned, typically using a higher-order measurement system in conjunction with one or more higher-order certified reference materials.

References for Appendix B

- ¹ ASTM. *Standard Practice for Estimating and Monitoring the Uncertainty of Test Results of a Test Method in a Single Laboratory Using a Control Sample Program*. ASTM E2554-07. West Conshohocken, PA, USA: ASTM International; 2007.
- ² ISO. *Measurement uncertainty for metrological applications – Repeated measurements and nested experiments*. ISO/TS 21749. Geneva, Switzerland: International Organization for Standardization; 2005.

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The quality management system approach applies a core set of “quality system essentials” (QSEs), basic to any organization, to all operations in any health care service’s path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager’s guide. The QSEs are as follows:

Organization	Personnel	Process Management	Nonconforming Event Management
Customer Focus	Purchasing and Inventory	Documents and Records	Assessments
Facilities and Safety	Equipment	Information Management	Continual Improvement

EP29-A addresses the QSE indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
						X C24 EP05 EP06 EP07 EP09 EP10 EP15 EP21	GP02	GP02		EP10	EP07

Related CLSI Reference Materials*

C24-A3	Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline—Third Edition (2006). This guideline provides definitions of analytical intervals, planning of quality control procedures, and guidance for quality control applications.
EP05-A2	Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition (2004). This document provides guidance for designing an experiment to evaluate the precision performance of quantitative measurement methods; recommendations on comparing the resulting precision estimates with manufacturers' precision performance claims and determining when such comparisons are valid; as well as manufacturers' guidelines for establishing claims.
EP06-A	Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (2003). This document provides guidance for characterizing the linearity of a method during a method evaluation; for checking linearity as part of routine quality assurance; and for determining and stating a manufacturer's claim for linear range.
EP07-A2	Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition (2005). This document provides background information, guidance, and experimental procedures for investigating, identifying, and characterizing the effects of interfering substances on clinical chemistry test results.
EP09-A2-IR	Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (Interim Revision) (2010). This document addresses procedures for determining the bias between two clinical methods, and the design of a method comparison experiment using split patient samples and data analysis.
EP10-A3	Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition (2006). This guideline provides experimental design and data analysis for preliminary evaluation of the performance of a measurement procedure or device.
EP15-A2	User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (2006). This document describes the demonstration of method precision and trueness for clinical laboratory quantitative methods utilizing a protocol designed to be completed within five working days or less.
EP21-A	Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline (2003). This document provides manufacturers and end users with a means to estimate total analytical error for an assay. A data collection protocol and an analysis method that can be used to judge the clinical acceptability of new methods using patient specimens are included. These tools can also monitor an assay's total analytical error by using quality control samples.
GP02-A5	Laboratory Documents: Development and Control; Approved Guideline—Fifth Edition (2006). This document provides guidance on development, review, approval, management, and use of policy, process, and procedure documents in the medical laboratory community.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

Active Membership (As of 1 January 2012)

Sustaining Members

Abbott
American Association for Clinical Chemistry
AstraZeneca Pharmaceuticals
Bayer Healthcare, LLC Diagnostic Division
BD
Beckman Coulter, Inc.
bioMérieux, Inc.
College of American Pathologists
Diagnostica Stago
GlaxoSmithKline
National Institute of Standards and Technology
Ortho-Clinical Diagnostics, Inc.
Pfizer Inc
Roche Diagnostics, Inc.

Professional Members

AAMI
American Association for Clinical Chemistry
American Association for Laboratory Accreditation
American Medical Technologists
American Society for Clinical Laboratory Science
American Society for Clinical Pathology
American Society for Microbiology
American Type Culture Collection
Association of Public Health Laboratories
Associazione Microbiologi Clinici Italiani (AMCLI)
British Society for Antimicrobial Chemotherapy
Canadian Society for Medical Laboratory Science
COLA
College of American Pathologists
College of Medical Laboratory Technologists of Ontario
College of Physicians and Surgeons of Saskatchewan
Critical Path Institute
ESCMD
Family Health International
Hong Kong Accreditation Service Innovation and Technology Commission
International Federation of Biomedical Laboratory Science
International Federation of Clinical Chemistry
Italian Society of Clin. Biochem. and Clin. Molec. Biology
JCCLS
National Society for Histotechnology, Inc.
Nova Scotia Association of Clinical Laboratory Managers
Ontario Medical Association Quality Management Program-Laboratory Service
RCPA Quality Assurance Programs Pty Limited
SIMeL
Sociedad Española de Bioquímica Clínica y Patología Molec.
Sociedade Brasileira de Análises Clínicas
Sociedade Brasileira de Patologia Clínica The Joint Commission
The Korean Society for Laboratory Medicine
World Health Organization

Government Members

Armed Forces Institute of Pathology
BC Centre for Disease Control
Canadian Science Center for Human and Animal Health
Centers for Disease Control and Prevention
Centers for Disease Control and Prevention - Ethiopia
Centers for Disease Control and Prevention - Namibia
Centers for Disease Control and Prevention - Nigeria
Centers for Disease Control and Prevention - Tanzania
Centers for Disease Control and Prevention - Zambia
Centers for Medicare & Medicaid Services
Centers for Medicare & Medicaid Services/CLIA Program
Chinese Committee for Clinical Laboratory Standards

Chinese Medical Association (CMA)
Clalit Health Services
Department of Veterans Affairs
DHSR/CLIA Certification
Diagnostic Accreditation Program
Ethiopian Health and Nutrition Research Institute
FDA Center for Veterinary Medicine
FDA Ctr. for Devices/Rad. Health
Health Canada
Institute of Tropical Medicine Dept. of Clinical Sciences
MA Dept. of Public Health Laboratories
Malaria Research Training Center
Marion County Public Health Department
Meuhedet Central Lab
Ministry of Health and Social Welfare - Tanzania
Mongolian Agency for Standardization and Metrology
Namibia Institute of Pathology
National Cancer Institute, OBBR, NIH
National Food Institute Technical University of Denmark
National Health Laboratory Service C/O F&M Import & Export Services
National HIV & Retrovirology Lab
Public Health Agency of Canada
National Institute of Health-Maputo, Mozambique
National Institute of Standards and Technology
National Pathology Accreditation Advisory Council
New York State Dept. of Health
Ontario Agency for Health Protection and Promotion
Pennsylvania Dept. of Health
SA Pathology
Saskatchewan Health-Provincial Laboratory
Scientific Institute of Public Health
State of Alabama
State of Wyoming Public Health Laboratory
The Nathan S. Kline Institute
University of Iowa, Hygienic Lab
US Naval Medical Research Unit #3
USAMC - AFRIMS

Industry Members

3M Medical Division
AB Diagnostic Systems GmBH
Abbott
Abbott Diabetes Care
Abbott Point of Care Inc.
Access Genetics
Aderans Research
AdvaMed
Akonni Biosystems
Ammirati Regulatory Consulting
Anapharm, Inc.
Aria Diagnostics
AspenBio Pharma, Inc.
Astellas Pharma
AstraZeneca Pharmaceuticals
Astute Medical, Inc.
Ativa Medical
Axis-Shield PoC AS
Bayer Healthcare, LLC Diagnostic Division
BD
BD Biosciences - San Jose, CA
BD Diagnostic Systems
BD Vacutainer Systems
Beaufort Advisors, LLC
Beckman Coulter Cellular Analysis Business Center
Beckman Coulter, Inc.
Beth Goldstein Consultant
Bio-Rad Laboratories, Inc.
Bio-Rad Laboratories, Inc. - France
Bioanalyse, Ltd.
Biocartis
BioDevelopment S.r.l.
Biohit Oyj.
Biomedica Laboratories SDN BHD
bioMérieux, Inc.
Blaine Healthcare Associates, Inc.
BRI Consultants Limited
Calloway Laboratories
Canon U.S. Life Sciences, Inc.
CBI Inc.
Cempra Pharmaceuticals, Inc.
Cepheid
Cerilliant Corp.
Compliance Insight, Inc.
Constitution Medical Inc
Controllab
Copan Diagnostics Inc.
Courtagen Life Sciences Inc.

Crescendo Bioscience
Cubist Pharmaceuticals, Inc.
Dahl-Chase Pathology Associates PA
Diagnostica Stago
DX Assays Pte Ltd.
Eiken Chemical Company, Ltd.
Elanco Animal Health
Elkin Simson Consulting Services
Emika Consulting
EndPoint Associates, LLC
Enigma Diagnostics
Eurofins Medinet
Evidia Biosciences Inc.
EXACT Sciences Corporation
Gen-Probe
Genefluidics
GlaxoSmithKline
Greiner Bio-One Inc.
Himedia Labs Ltd
HistoGenex N.V.
Hospital Sungai Buloh
Icon Laboratories, Inc.
Innovotech, Inc.
Instrumentation Laboratory
Integrated BioBank
IntelligentMDx, Inc.
Intuity Medical
ITC Corp
Japan Assn. of Clinical Reagents Industries
Johnson & Johnson Pharmaceutical Research & Develop., L.L.C.
Kaiser Permanente
KoreaBIO
Krouwer Consulting
Lab PMM
Laboratory Specialists, Inc.
LifeLabs
LifeScan, Inc.
Liofilchem SRL
LipoScience, Inc.
Maine Standards Company, LLC
Marketing MicroScan & Molecular Korea-Siemens Healthcare
Masimo Corp.
Masimo Labs
Mbio Diagnostics, Inc.
MDxHealth SA
Medical Device Consultants, Inc.
Merck & Company, Inc.
Meril Limited
Meso Scale Diagnostics, LLC.
Micromyx, LLC
Molecular Response
Moscow Antidoping Agency
Nanosphere, Inc.
Nihon Kohden Corporation
Nissui Pharmaceutical Co., Ltd.
NJK & Associates, Inc.
NorDx - Scarborough Campus
Nova Biomedical Corporation
NovaBiotics
Novartis Institutes for Biomedical Research
Optimer Pharmaceuticals, Inc.
Ortho-Clinical Diagnostics, Inc.
Ortho-McNeil, Inc.
Oxysure, Inc.
Paratek Pharmaceuticals, Inc.
PathCare Pathology Laboratory
PerkinElmer Genetics, Inc.
Pfizer Animal Health
Pfizer Inc
Pfizer Italia Srl
Phadia AB
Philips Healthcare Incubator
PPD
ProteoGenix, Inc.
QML Pathology
Quotient Bioresearch Ltd.
R-Biopharm AG
Radiometer America, Inc.
Roche Diagnostics GmbH
Roche Diagnostics, Inc.
Roche Molecular Systems
RPL Laboratory Solutions, Inc.
DBA RPL Compliance Solutions
Sanofi Pasteur
Sarstedt, Inc.
Sekisui Diagnostics
Seventh Sense Biosystems
Siemens Healthcare Diagnostics Inc.
Siemens Healthcare Diagnostics Products GmbH
Soloy Laboratory Consulting Services, Llc
SomaLogic
Sphere Medical Holding Limited
Streck Laboratories, Inc.
Super Religare Laboratories Ltd
Sysmex America, Inc.
Sysmex Corporation - Japan
Tetraphase Pharmaceuticals

The Clinical Microbiology Institute
The Medicines Company
TheraDoc
Theranos
Theravance Inc.
Thermo Fisher Scientific
Thermo Fisher Scientific, Oxoid Products
Thermo Fisher Scientific, Remel
Transasia Bio-Medicals Limited
Tulip Group
Ventana Medical Systems Inc.
VeracYTE, Inc.
Vivacta
Watson Pharmaceuticals
Wellstat Diagnostics, LLC
XDX, Inc.

Associate Active Members

31st Medical Group SGSL (AE)
3rd Medical Group (AK)
48th Medical Group/MDSS RAF Lakenheath (AE)
55th Medical Group/SGSAL (NE)
59th MDW/859th MDTs/MTL Wilford Hall Medical Center (TX)
82 MDG/SGSCL Sheppard AFB (TX)
Academisch Ziekenhuis-VUB UZ Brussel (Belgium)
ACL Laboratories (IL)
ACL Laboratories (WI)
Adams County Hospital (OH)
Adena Regional Medical Center Hospital (OH)
Affiliated Laboratory, Inc. (ME)
Akron Children's Hospital (OH)
Al Ain Hospital (Abu Dhabi, United Arab Emirates)
Al Hada Armed Forces Hospital/TAIF/KSA (Saudi Arabia)
Al Noor Hospital (United Arab Emirates)
Al Rabha Hospital (United Arab Emirates)
Alameda County Medical Center (CA)
Albany Medical Center Hospital (NY)
Albemarle Hospital (NC)
Alberta Health Services (AB, Canada)
Alexandra Hospital (Singapore)
Alfred I. du Pont Hospital for Children (FL)
All Children's Hospital (FL)
Allegiance Health (MI)
Alpena Regional Medical Center (MI)
Alta Bates Summit Medical Center (CA)
Alverno Clinical Laboratories, Inc. (IN)
American Esoteric Laboratories (AEL) (TN)
American University of Beirut Medical Center (NJ)
Anand Diagnostic Laboratory (India)
Anne Arundel Medical Center (MD)
Antech Diagnostics (CA)
Antelope Valley Hospital District (CA)
Appalachian Regional Healthcare System (NC)
Arkansas Dept of Health Public Health Laboratory (AR)
Arkansas Methodist Medical Center (AR)
ARUP Laboratories (UT)
Asan Medical Center (Korea, Republic Of)
Asante Health System (OR)
Ashley County Medical Center (AR)
Asiri Group of Hospitals Ltd. (Sri Lanka)
Aspen Valley Hospital (CO)
ASPETAR (Qatar Orthopedic and Sports Medicine Hospital) (Qatar)
Aspirus Wausau Hospital (WI)
Atlantic Diagnostics Laboratories (PA)
Atrium Medical Center (OH)
Auburn Regional Medical Center (WA)
Augusta Health (VA)
Aultman Hospital (OH)
Avera McKennan Laboratory (SD)
AZ Sint-Jan (Belgium)
Azienda Ospedale Di Lecco (Italy)
Baptist Hospital of Miami (FL)
Baptist Memorial Health Care Corporation - Hospital Laboratories Works (TN)
Barnes-Jewish Hospital (MO)
Bassett Healthcare (NY)
Baton Rouge General (LA)
Baxter Regional Medical Center (AR)
BayCare Health System (FL)
Baylor Health Care System (TX)
Bayou Pathology, APMC (LA)
Baystate Medical Center (MA)
BC Biomedical Laboratories (BC, Canada)
Beloit Memorial Hospital (WI)
Beth Israel Medical Center (NY)
Bio-Reference Laboratories (NJ)

Blanchard Valley Hospital (OH)	Contra Costa Regional Medical Center (CA)	Health Network Lab (PA)	Laboratória Médico Santa Luzia LTDA (Brazil)
Bon Secours Health Partners (VA)	Cook Children's Medical Center (TX)	Health Sciences Research Institute (Japan)	Laboratory Alliance of Central New York (NY)
Bonnyville Health Center (AB, Canada)	Cookeville Regional Medical Center (TN)	Health Waikato (New Zealand)	Laboratory Corporation of America (NJ)
Boston Medical Center (MA)	Cornwall Community Hospital (ON, Canada)	Heartland Health (MO)	Laboratory Medicin Dalarna (Dalarna, Sweden)
Boulder Community Hospital (CO)	Covance CLS (IN)	Heidelberg Army Hospital (AE)	LabPlus Auckland District Health Board (New Zealand)
Boyce & Bynum Pathology Labs (MO)	Covenant Medical Center (TX)	Helen Hayes Hospital (NY)	LAC/USC Medical Center (CA)
Brant Community Healthcare System/Brant General Hospital (Ontario, Canada)	Creighton Medical Lab (NE)	Helix (Russian Federation)	Lafayette General Medical Center (LA)
Bremerton Naval Hospital (WA)	Crozer-Chester Medical Center (PA)	Henry Ford Hospital (MI)	Lakeland Regional Medical Center (FL)
Brian All Good Community Hospital/121 Combat (AP)	Cumberland Medical Center (TN)	Henry M. Jackson Foundation for the Advancement of Military Medicine- MD (MD)	Lancaster General Hospital (PA)
Bridgeport Hospital (CT)	Darwin Library NT Territory Health Services (NT, Australia)	Hi-Desert Medical Center (CA)	Landstuhl Regional Medical Center (Germany)
Brooke Army Medical Center (TX)	David Grant Medical Center (CA)	Highlands Medical Center (AL)	Langley Air Force Base (VA)
Broward General Medical Center (FL)	Daviess Community Hospital (IN)	HJF Naval Infectious Diseases Diagnostic Laboratory (MD)	LeBonheur Children's Hospital (TN)
Cadham Provincial Laboratory-MB Health (MB, Canada)	Deaconess Hospital Laboratory (IN)	Hoag Memorial Hospital Presbyterian (CA)	Legacy Laboratory Services (OR)
Calgary Laboratory Services (AB, Canada)	Dean Medical Center (WI)	Hoboken University Medical Center (NJ)	Letherbridge Regional Hospital (AB, Canada)
Cambridge Health Alliance (MA)	DHHS NC State Lab of Public Health (NC)	Holy Cross Hospital (MD)	Lewis-Gale Medical Center (VA)
Cape Fear Valley Medical Center Laboratory (NC)	DiagnoSearch Life Sciences Inc. (Maharashtra, India)	Holy Name Hospital (NJ)	Lexington Medical Center (SC)
Capital Coast Health (New Zealand)	Diagnostic Laboratory Services, Inc. (HI)	Holy Spirit Hospital (PA)	L'Hotel-Dieu de Québec (PQ, Canada)
Capital Health System Mercer Campus (NJ)	Diagnostic Services of Manitoba (MB, Canada)	Hôpital de la Cité-de-La-Santé De Laval (Quebec, Canada)	Licking Memorial Hospital (OH)
Caritas Norwood Hospital (MA)	Dimensions Healthcare System Prince George's Hospital Center (MD)	Hôpital du Haut-Richelieu (PQ, Canada)	LifeBridge Health Sinai Hospital (MD)
Carl R. Darnall Army Medical Center Department of Pathology (TX)	DMC University Laboratories (MI)	Hôpital Maisonneuve-Rosemont (PQ, Canada)	Lifelabs Medical Laboratory Services (BC, Canada)
Carolina Medical Laboratory (NC)	Drake Center (OH)	Hôpital Santa Cabrini Ospedale (PQ, Canada)	Lifeline Hospital (United Arab Emirates)
Carolinas Healthcare System (NC)	Driscoll Children's Hospital (TX)	Horizon Health Network (N.B., Canada)	Loma Linda University Medical Center (LLUMC) (CA)
Carpermor S.A. de C.V. (D.F., Mexico)	DUHS Clinical Laboratories Franklin Site (NC)	Hospital Albert Einstein (SP, Brazil)	Long Beach Memorial Medical Center- LBMMC (CA)
Catholic Health Initiatives (KY)	Dynacare Laboratory (WI)	Hospital Sacre-Coeur de Montreal (Quebec, Canada)	Long Island Jewish Medical Center (NY)
Cedars-Sinai Medical Center (CA)	Dynacare NW, Inc - Seattle (WA)	Hôtel-Dieu Grace Hospital Library (ON, Canada)	Louisiana Office of Public Health Laboratory (LA)
Cenetrion Diagnostics (TX)	DynaLIFE (AB, Canada)	Hunter Area Pathology Service (Australia)	Louisiana State University Medical Ctr. (LA)
Central Baptist Hospital (KY)	E. A. Conway Medical Center (LA)	Hunter Labs (CA)	Lower Columbia Pathologists, P.S. (WA)
Central Kansas Medical Center (KS)	East Georgia Regional Medical Center (GA)	Huntington Memorial Hospital (CA)	Lower Mainland Laboratories (BC, Canada)
Centre Hospitalier Anna-Laberge (Quebec, Canada)	East Kootenay Regional Hospital Laboratory-Interior Health (BC, Canada)	Imelda Hospital (Belgium)	Lyndon B. Johnson General Hospital (TX)
Centre Hospitalier Regional De Trois Rivières (PQ, Canada)	East Texas Medical Center-Pittsburg (TX)	Indian River Memorial Hospital (FL)	Maccabi Medical Care and Health Fund (Israel)
Centro Médico Imbanaco (Colombia)	Eastern Health - Health Sciences Centre (NL, Canada)	Indiana University Health Bloomington Hospital (IN)	Madigan Army Medical Center (WA)
Chaleur Regional Hospital (NB, Canada)	Eastern Health Pathology (Victoria, Australia)	Indiana University Health Care- Pathology Laboratory (IN)	Mafrga Hospital (United Arab Emirates)
Chang Gung Memorial Hospital (Taiwan)	Easton Hospital (PA)	Inova Central Laboratory (VA)	Magnolia Regional Health Center (MS)
Changhua Christian Hospital (Taiwan)	Edward Hospital (IL)	Institut fur Stand. und Dok. im Med. Lab. (Germany)	Main Line Clinical Laboratories, Inc. Lankenau Hospital (PA)
Changi General Hospital (Singapore)	Effingham Hospital (GA)	Institut National de Santé Publique Du Quebec Centre de Doc. - INSPQ (PQ, Canada)	Makerere University Walter Reed Project Makerere University Medical School (Uganda)
Chatham - Kent Health Alliance (ON, Canada)	Elmhurst Hospital Center (NY)	Institute Health Laboratories (PR)	Marquette General Hospital (MI)
Chesapeake General Hospital (VA)	Emory University Hospital (GA)	Institute of Clinical Pathology and Medical Research (Australia)	Marshall Clinic (WI)
Chester County Hospital (PA)	Evangelical Community Hospital (PA)	Institute of Laboratory Medicine Landsipitali Univ. Hospital (Iceland)	Martha Jefferson Hospital (VA)
Children's Healthcare of Atlanta (GA)	Evans Army Community Hospital (CO)	Institute of Medical & Veterinary Science (SA, Australia)	Martin Luther King, Jr./Drew Medical Center (CA)
Childrens Hosp.- Kings Daughters (VA)	Exeter Hospital (NH)	Integrated Regional Laboratories South Florida (HCA) (VA)	Martin Memorial Health Systems (FL)
Children's Hospital & Research Center At Oakland (CA)	Exosome Diagnostics, Inc. (MN)	Intermountain Health Care Lab Services (UT)	Mary Hitchcock Memorial Hospital (NH)
Childrens Hospital Los Angeles (CA)	Federal Medical Center (MN)	International Health Management Associates, Inc. (IL)	Mary Washington Hospital (VA)
Children's Hospital Medical Center (OH)	First Health of the Carolinas Moore Regional Hospital (NC)	Irwin Army Community Hospital (KS)	Mater Health Services - Pathology (Australia)
Children's Hospital of Central California (CA)	Fletcher Allen Health Care (VT)	Jackson County Memorial Hospital (OK)	Maxwell Air Force Base (AL)
Children's Hospital of Orange County (CA)	Fleury S.A. (Brazil)	Jackson Memorial Hospital (FL)	Mayo Clinic (MN)
Children's Hospital of Philadelphia (PA)	Florida Hospital (FL)	Jackson Purchase Medical Center (KY)	MCG Health (GA)
Childrens Hospital of Wisconsin (WI)	Fox Chase Cancer Center (PA)	Jessa Ziekenhuis VZW (Belgium)	Meadows Regional Medical Center (GA)
Children's Hospitals and Clinics (MN)	Fraser Health Authority Royal Columbian Hospital Site (BC, Canada)	John C. Lincoln Hospital - N.MT. (AZ)	Medical Center Hospital (TX)
Children's Medical Center (OH)	Fundação Faculdade de Medicina (SP, Brazil)	John F. Kennedy Medical Center (NJ)	Medical Center of Louisiana At NO- Charity (LA)
Children's Medical Center (TX)	Gamma-Dynacare Laboratories (ON, Canada)	John H. Stroger, Jr. Hospital of Cook County (IL)	Medical Centre Ljubljana (Slovenia)
Christiana Care Health Services (DE)	Garden City Hospital (MI)	John Muir Health (CA)	Medical College of Virginia Hospital (VA)
CHU - Saint Pierre (Belgium)	Garfield Medical Center (CA)	John T. Mather Memorial Hospital (NY)	Medical University Hospital Authority (SC)
CHU Sainte-Justine (Quebec, Canada)	Gaston Memorial Hospital (NC)	Johns Hopkins Medical Institutions (MD)	Memorial Hermann Healthcare System (TX)
CHUM Hospital Saint-Luc (Quebec, Canada)	Geisinger Medical Center (PA)	Johns Hopkins University (MD)	Memorial Medical Center (IL)
CHW-St. Mary's Medical Center (CA)	Genesis Healthcare System (OH)	Johnson City Medical Center Hospital (TN)	Memorial Medical Center (PA)
City of Hope National Medical Center (CA)	George Washington University Hospital (DC)	JPS Health Network (TX)	Memorial Regional Hospital (FL)
Clearstone Central Laboratories (ON, Canada)	Gestión de Calidad (Argentina)	Kailos Genetics (AL)	Mercy Franciscan Mt. Airy (OH)
Cleveland Clinic (OH)	Gettysburg Hospital (PA)	Kaiser Permanente (MD)	Mercy Hospital & Medical Center (IL)
Cleveland Heartlab, LLC (OH)	Ghent University Hospital (Belgium)	Kaiser Permanente (OH)	Methodist Dallas Medical Center (TX)
Clinica Alemana De Santiago (Chile)	Good Shepherd Medical Center (TX)	Kaiser Permanente Medical Care (CA)	Methodist Healthcare (North) (TN)
Clinical and Laboratory Standards Institute (PA)	Grana S.A. (TX)	Kaohsiun Chang Gung Memorial Hospital (Taiwan)	Methodist Hospital (TX)
Clinical Labs of Hawaii (HI)	Grand River Hospital (ON, Canada)	Kenora-Rainy River Reg. Lab. Program (ON, Canada)	Methodist Hospital (TX)
Clinical Trials Service (Belgium)	Grand Strand Regional Medical Center (SC)	KFMC (Saudi Arabia)	Methodist Hospital Park Nicollet Health Services (MN)
College of Physicians and Surgeons of Alberta (AB, Canada)	Grey Bruce Regional Health Center (ON, Canada)	King Abdulaziz Hospital, Al Ahsa Dept. of Pathology & Laboratory Medicine (Al-Hasa, Saudi Arabia)	Methodist Hospital Pathology (NE)
Collingwood General & Marine Hospital (ON, Canada)	Group Health Cooperative (WA)	King Fahad National Guard Hospital KAMC - NGH (Saudi Arabia)	Methodist Willowbrook Hospital (TX)
Commonwealth of Kentucky (KY)	Gundersen Lutheran Medical Center (WI)	King Fahad Specialist Hospital- Dammam, K.S.A. (Eastern Region, Saudi Arabia)	MetroHealth Medical Center (OH)
Commonwealth of Virginia (DCLS) (VA)	Guthrie Clinic Laboratories (PA)	King Faisal Specialist Hospital & Research Center (Saudi Arabia)	Metropolitan Hospital Center (NY)
Community Hospital (IN)	Hôtel-Dieu de Lévis (PQ, Canada)	King Hussein Cancer Center (Jordan)	Metropolitan Medical Laboratory, PLC (IA)
Community Hospital of the Monterey Peninsula (CA)	Halton Healthcare Services (ON, Canada)	Kingston General Hospital (ON, Canada)	Miami Children's Hospital (FL)
Community Medical Center (NJ)	Hamilton Regional Laboratory Medicine Program - St. Joseph's (ON, Canada)		Mid Michigan Medical Center - Midland (MI)
Community Memorial Hospital (WI)	Hanover General Hospital (PA)		Middelheim General Hospital (Belgium)
Complexe Hospitalier de la Sagamie (Quebec, Canada)	Harford Memorial Hospital (MD)		Middlesex Hospital (CT)
CompuNet Clinical Laboratories Quest Diagnostics JV (OH)	Harris Methodist Fort Worth (TX)		Minneapolis Medical Research Foundation (MN)
Concord Hospital (NH)	Harris Methodist Hospital Southwest (TX)		Mississippi Baptist Medical Center (MS)
Consultants Laboratory of WI LLC (WI)	Hartford Hospital (CT)		

Mississippi Public Health Lab (MS)	Queensland Health Pathology Services (Australia)	St. Michael's Medical Center, Inc. (NJ)	University Hospital Center Sherbrooke (CHUS) (Quebec, Canada)
Monongalia General Hospital (WV)	Queensway Carleton Hospital (ON, Canada)	St. Tammany Parish Hospital (LA)	University Medical Center at Princeton (NJ)
Montreal General Hospital (Quebec, Canada)	Quest Diagnostics, Incorporated (CA)	Stanford Hospital and Clinics (CA)	University of Alabama Hospital Lab (AL)
Morehead Memorial Hospital (NC)	Quintiles Laboratories, Ltd. (GA)	Stanton Territorial Health Authority (NT, Canada)	University of Chicago Hospitals Laboratories (IL)
Mowasat Hospital (GA, Saudi Arabia)	Rady Children's Hospital San Diego (CA)	State of Connecticut Department of Public Health (CT)	University of Colorado Health Sciences Center (CO)
Mt. Carmel Health System (OH)	Ramathibodi Hospital (Thailand)	State of Ohio/Corrections Medical Center Laboratory (OH)	University of Colorado Hospital (CO)
Mt. Sinai Hospital (ON, Canada)	Redington-Fairview General Hospital (ME)	State of Washington Public Health Labs (WA)	University of Illinois Medical Center (IL)
Mt. Sinai Hospital - New York (NY)	Regions Hospital (MN)	Stillwater Medical Center (OK)	University of Iowa Hospitals and Clinics (IA)
Naples Community Hospital (FL)	Reid Hospital & Health Care Services (IN)	Stony Brook University Hospital (NY)	University of Kentucky Medical Center (KY)
Nassau County Medical Center (NY)	Reinier De Graaf Groep (Netherlands)	Stormont-Vail Regional Medical Ctr. (KS)	University of Maryland Medical System (MD)
National B Virus Resource Laboratory (GA)	Renown Regional Medical Center (NV)	Sudbury Regional Hospital (ON, Canada)	University of Minnesota Medical Center- Fairview (MN)
National Cancer Center (Korea, Republic Of)	Research Medical Center (MO)	Sunnybrook Health Sciences Centre (ON, Canada)	University of Missouri Hospital (MO)
National Institutes of Health, Clinical Center (MD)	Response Genetics, Inc. (CA)	Swedish Edmonds Hospital (WA)	University of Pennsylvania Health System (PA)
National Naval Medical Center (MD)	RIPAS Hospital (Brunei-Mauria, Brunei Darussalam)	Swedish Medical Center (CO)	University of Pittsburgh Medical Center (PA)
National University Hospital Department of Laboratory Medicine (Singapore)	Riverside County Regional Medical Center (CA)	Sydney South West Pathology Service - Liverpool Hospital (NSW, Australia)	University of Texas Health Center (TX)
National University of Ireland, Galway (NUIJG) (Ireland)	Riverside Health System (VA)	T.J. Samson Community Hospital (KY)	University of the Ryukyus (Japan)
Nationwide Children's Hospital (OH)	Riyadh Armed Forces Hospital, Sulaymania (Saudi Arabia)	Taichung Veterans General Hospital (Taiwan)	University of Virginia Medical Center (VA)
Naval Hospital Oak Harbor (WA)	Rockford Memorial Hospital (IL)	Taiwan Society of Laboratory Medicine (Taiwan)	UPMC Bedford Memorial (PA)
Naval Medical Center Portsmouth (VA)	Royal Victoria Hospital (ON, Canada)	Tallaght Hospital (Ireland)	US Naval Hospital Naples
Naval Medical Clinic Hawaii (HI)	SAAD Specialist Hospital (Saudi Arabia)	Tartu University Clinics (Estonia)	UZ-KUL Medical Center (Belgium)
NB Department of Health (NB, Canada)	Sacred Heart Hospital (FL)	Temple Univ. Hospital - Parkinson Pav. (PA)	VA (Asheville) Medical Center (NC)
New England Baptist Hospital (MA)	Sacred Heart Hospital (WI)	Tenet Healthcare (PA)	VA (Bay Pines) Medical Center (FL)
New England Fertility Institute (CT)	Sahlgrenska Universitetssjukhuset (Sweden)	Texas Children's Hospital (TX)	VA (Central Texas) Veterans Health Care System (TX)
New England Sinai Hospital (MA)	Saint Francis Hospital & Medical Center (CT)	Texas Department of State Health Services (TX)	VA (Chillicothe) Medical Center (OH)
New Lexington Clinic (KY)	Saint Mary's Regional Medical Center (NV)	Texas Health Presbyterian Hospital Dallas (TX)	VA (Cincinnati) Medical Center (OH)
New York Presbyterian Hospital (NY)	Saints Memorial Medical Center (MA)	The Brooklyn Hospital Center (NY)	VA (Dallas) Medical Center (TX)
New York Presbyterian Hospital (NY)	Salem Memorial District Hospital (MO)	The Charlotte Hungerford Hospital (CT)	VA (Dayton) Medical Center (OH)
New York University Medical Center (NY)	Sampson Regional Medical Center (NC)	The Children's Mercy Hospital (MO)	VA (Hines) Medical Center (IL)
Newark Beth Israel Medical Center (NJ)	Samsung Medical Center (Korea, Republic Of)	The Cooley Dickinson Hospital, Inc. (MA)	VA (Indianapolis) Medical Center (IN)
Newfoundland Public Health Laboratory (NL, Canada)	San Francisco General Hospital- University of California San Francisco (CA)	The Credit Valley Hospital (ON, Canada)	VA (Iowa City) Medical Center (IA)
North Carolina Baptist Hospital (NC)	Sanford USD Medical Center (SD)	The Hospital for Sick Children (ON, Canada)	VA (Miami) Medical Center (FL)
North District Hospital (China)	Santa Clara Valley Medical Center (CA)	The Medical Center of Aurora (CO)	VA (San Diego) Medical Center (CA)
North Mississippi Medical Center (MS)	SARL Laboratoire Caron (France)	The Michener Inst. for Applied Health Sciences (ON, Canada)	VA (Tampa) Hospital (FL)
North Shore Hospital Laboratory (New Zealand)	Scott & White Memorial Hospital (TX)	The Naval Hospital of Jacksonville (FL)	VA (Wilmington) Medical Center (DE)
North Shore-Long Island Jewish Health System Laboratories (NY)	Seattle Children's Hospital/Children's Hospital and Regional Medical Center (WA)	The Nebraska Medical Center (NE)	Vancouver Island Health Authority (SI) (BC, Canada)
Northridge Hospital Medical Center (CA)	Seoul National University Hospital (Korea, Republic Of)	The Ottawa Hospital (ON, Canada)	Vanderbilt University Medical Center (TN)
Northside Hospital (GA)	Seoul St. Mary's Hospital (Korea, Republic Of)	The Permanente Medical Group (CA)	Verinata Health, Inc. (CA)
Northside Medical Center (OH)	Seton Healthcare Network (TX)	The Toledo Hospital (OH)	Via Christi Regional Medical Center (KS)
Northwest Texas Hospital (TX)	Seton Medical Center (CA)	The University of Texas Medical Branch (TX)	Viracor-IBT Reference Laboratory (MO)
Northwestern Memorial Hospital (IL)	Sharp Health Care Laboratory Services (CA)	Thomas Jefferson University Hospital, Inc. (PA)	Virginia Regional Medical Center (MN)
Norton Healthcare (KY)	Sheik Kalifa Medical City (United Arab Emirates)	Timmins and District Hospital (ON, Canada)	Virtua - West Jersey Hospital (NJ)
Ochsner Clinic Foundation (LA)	Shore Memorial Hospital (NJ)	Tokyo Metro. Res. Lab of Public Health (Japan)	WakeMed (NC)
Ohio State University Hospitals (OH)	Singapore General Hospital (Singapore)	Touro Infirmary (LA)	Walter Reed Army Medical Center (DC)
Ohio Valley Medical Center (WV)	Slotervaart Ziekenhuis (Netherlands)	TriCore Reference Laboratories (NM)	Warren Hospital (NJ)
Onze Lieve Vrouweziekenhuis (Belgium)	South Bend Medical Foundation (IN)	Trident Medical Center (SC)	Washington Hospital Center (DC)
Ordre Professionnel Des Technologistes Médicaux Du Quebec (Quebec, Canada)	South Eastern Area Laboratory Services (NSW, Australia)	Trinity Medical Center (AL)	Washington Hospital Healthcare System (CA)
Orebro University Hospital (Sweden)	South Miami Hospital (FL)	Trinity Muscatine (IA)	Waterbury Hospital (CT)
Orlando Health (FL)	Southern Community Laboratories (Canterbury, New Zealand)	Tripler Army Medical Center (HI)	Waterford Regional Hospital (Ireland)
Ospedale Casa Sollievo Della Sofferenza - IRCCS (Italy)	Southern Health Care Network (Australia)	Tuen Mun Hospital, Hospital Authority (China)	Weed Army Community Hospital Laboratory (CA)
Our Lady's Hospital For Sick Children (Ireland)	Southwest Healthcare System (CA)	Tufts Medical Center Hospital (MA)	Weirton Medical Center (WV)
Palmetto Baptist Medical Center (SC)	Southwestern Medical Center (OK)	Tulane Medical Center Hospital & Clinic (LA)	West Jefferson Medical Center (LA)
Pamela Youde Nethersole Eastern Hospital (Hong Kong East Cluster) (Hong Kong)	Spectra East (NJ)	Turku University Central Hospital (Finland)	West Penn Allegheny Health System- Allegheny General Hospital (PA)
Pathgroup (TN)	Spectra Laboratories (CA)	Twin Lakes Regional Medical Center (KY)	West Shore Medical Center (MI)
Pathlab (IA)	St. Agnes Healthcare (MD)	UCI Medical Center (CA)	West Valley Medical Center Laboratory (ID)
Pathology and Cytology Laboratories, Inc. (KY)	St. Anthony Hospital (OK)	UCLA Medical Center Clinical Laboratories (CA)	Westchester Medical Center (NY)
Pathology Associates Medical Lab. (WA)	St. Barnabas Medical Center (NJ)	UCSD Medical Center (CA)	Western Baptist Hospital (KY)
Pathology Inc. (CA)	St. Elizabeth Community Hospital (CA)	UCSF Medical Center China Basin (CA)	Western Healthcare Corporation (NL, Canada)
Penn State Hershey Medical Center (PA)	St. Eustache Hospital (Quebec, Canada)	UMC of El Paso- Laboratory (TX)	Wheaton Franciscan Laboratories (WI)
Pennsylvania Hospital (PA)	St. Francis Hospital (SC)	UMC of Southern Nevada (NV)	Wheeling Hospital (WV)
Peterborough Regional Health Centre (ON, Canada)	St. Francis Memorial Hospital (CA)	UNC Hospitals (NC)	White Memorial Medical Center (CA)
PHS Indian Hospital - Pine Ridge (SD)	St. John Hospital and Medical Center (MI)	Unidad De Patología Clínica (Mexico)	Whitehorse General Hospital (YT, Canada)
Piedmont Hospital (GA)	St. John's Hospital & Health Center (CA)	Union Clinical Laboratory (Taiwan)	William Beaumont Army Medical Center (TX)
Pitt County Memorial Hospital (NC)	St. John's Mercy Medical Center (MO)	United Christian Hospital (Kowloon, Hong Kong)	William Beaumont Hospital (MI)
Potomac Hospital (VA)	St. John's Regional Health Center (MO)	United States Air Force School of Aerospace Medicine / PHE (OH)	William Osler Health Centre (ON, Canada)
Prairie Lakes Hospital (SD)	St. Jude Children's Research Hospital (TN)	Universitair Ziekenhuis Antwerpen (Belgium)	Winchester Hospital (MA)
Presbyterian Hospital - Laboratory (NC)	St. Luke's Hospital (IA)	University College Hospital (Ireland)	Winn Army Community Hospital (GA)
Presbyterian/St. Luke's Medical Center (CO)	St. Luke's Hospital (PA)	University Hospital (GA)	Wishard Health Sciences (IN)
Prince of Wales Hospital (Hong Kong)	St. Mary Medical Center (CA)		Womack Army Medical Center Department of Pathology (NC)
Princess Margaret Hospital (Hong Kong, China)	St. Mary's Hospital (WI)		Womens and Childrens Hospital (LA)
Providence Alaska Medical Center (AK)			York Hospital (PA)
Providence Health Services, Regional Laboratory (OR)			Yukon-Kuskokwim Delta Regional Hospital (AK)
Provincial Laboratory for Public Health (AB, Canada)			
Queen Elizabeth Hospital (P.E.I., Canada)			
Queen Elizabeth Hospital (China)			

Explore the Latest Offerings From CLSI!

As we continue to set the global standard for quality in laboratory testing, we are adding products and programs to bring even more value to our members and customers.



By becoming a CLSI member, your laboratory will join 1,600+ other influential organizations all working together to further CLSI's efforts to improve health care outcomes. You can play an active role in raising global laboratory testing standards—in your laboratory, and around the world.

Find out which membership option is best for you at www.clsi.org/membership.



Find what your laboratory needs to succeed! CLSI U provides convenient, cost-effective continuing education and training resources to help you advance your professional development. We have a variety of easy-to-use, online educational resources that make eLearning stress-free and convenient for you and your staff.

See our current educational offerings at www.clsi.org/education.



When laboratory testing quality is critical, standards are needed and there is no time to waste. eCLIPSE™ Ultimate Access, our cloud-based online portal of the complete library of CLSI standards, makes it easy to quickly find the CLSI resources you need.

Learn more and purchase eCLIPSE at cls.org/eCLIPSE.

For more information, visit www.clsi.org today.



950 West Valley Road, Suite 2500, Wayne, PA 19087 USA

P: +1.610.688.0100 **Toll Free (US):** 877.447.1888 F: +1.610.688.0700

E: customerservice@clsi.org www.clsi.org

PRINT ISBN 1-56238-787-1

ELECTRONIC ISBN 1-56238-788-X