CLINICAL AND LABORATORY STANDARDS INSTITUTE®

September 2014

EP15-A3

User Verification of Precision and Estimation of Bias; Approved Guideline—Third Edition

This document describes the estimation of imprecision and of bias for clinical laboratory quantitative measurement procedures using a protocol that can be completed within as few as five days.

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 clinical 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 clinical 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 addressed according to the consensus process by a committee of experts.

Appeals Process

If it is believed that an objection has not been adequately addressed, the process for appeals is documented in the CLSI Standards Development Policies and Process document.

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 further 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: 610.688.0100
F: 610.688.0700
www.clsi.org
standard@clsi.org

ISBN 1-56238-965-3 (Print)
ISBN 1-56238-966-1 (Electronic)
ISSN 1558-6502 (Print)
ISSN 2162-2914 (Electronic)

EP15-A3
Vol. 34 No. 12
Replaces EP15-A2
Vol. 25 No. 17

Volume 34 Number 12

User Verification of Precision and Estimation of Bias; Approved Guideline—Third Edition

R. Neill Carey, PhD, FACB
A. Paul Durham
Walter W. Hauck, PhD
Anders Kallner, MD, PhD
Marina V. Kondratovich, PhD
Jonathan Guy Middle, PhD
James F. Pierson-Perry
Merle B. Smith, MBA, MS, MT(ASCP)
Aparna Srinivasan, PhD

Abstract

Clinical and Laboratory Standards Institute document EP15-A3—*User Verification of Precision and Estimation of Bias; Approved Guideline—Third Edition* describes the verification of precision claims and estimation of relative bias for quantitative methods performed within the laboratory. Included are guidelines for duration, experimental designs, materials, data analysis summarization, and interpretation—techniques adaptable for the widest possible range of analytes and device complexity. A balance is created in the document between the complexity of design and formulae, and the simplicity of operation. The protocol is designed to be completed within five working days based on a uniform experimental design yielding estimates of imprecision and bias.

Clinical and Laboratory Standards Institute (CLSI). *User Verification of Precision and Estimation of Bias; Approved Guideline—Third Edition*. CLSI document EP15-A3 (ISBN 1-56238-965-3 [Print]; ISBN 1-56238-966-1 [Electronic]). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2014.

Suggested Citation

CLSI. *User Verification of Precision and Estimation of Bias; Approved Guideline—Third Edition*. CLSI document EP15-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.

Proposed Guideline
December 1998

Approved Guideline
December 2001

Approved Guideline—Second Edition
June 2005

Second Printing
April 2006

Approved Guideline—Third Edition
September 2014

ISBN 1-56238-965-3 (Print)
ISBN 1-56238-966-1 (Electronic)
ISSN 1558-6502 (Print)
ISSN 2162-2914 (Electronic)

Committee Membership

Consensus Committee on Evaluation Protocols

James F. Pierson-Perry
Chairholder
Siemens Healthcare Diagnostics, Inc.
Newark, Delaware, USA

Mitchell G. Scott, PhD
Vice-Chairholder
Barnes-Jewish Hospital
St. Louis, Missouri, USA

Karl De Vore
Bio-Rad Laboratories
Irvine, California, USA

Robert J. McEnroe, PhD
Roche Diagnostics, Inc.
Indianapolis, Indiana, USA

James H. Nichols, PhD, DABCC, FACB
Vanderbilt University Medical Center
Nashville, Tennessee, USA

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

Megan E. Sawchuk, MT(ASCP)
Centers for Disease Control and Prevention
Atlanta, Georgia, USA

Document Development Committee on Verification of Performance for Precision and Trueness

R. Neill Carey, PhD, FACB
Chairholder
Peninsula Regional Medical Center
Salisbury, Maryland, USA

Walter W. Hauck, PhD
USP
Rockville, Maryland, USA

Anders Kallner, MD, PhD
Karolinska Hospital
Stockholm, Sweden

Marina V. Kondratovich, PhD
FDA Center for Devices
and Radiological Health
Silver Spring, Maryland, USA

Merle B. Smith, MBA, MS, MT(ASCP)
Siemens Healthcare Diagnostics, Inc.
Newark, Delaware, USA

Aparna Srinivasan, PhD
Abaxis
Union City, California, USA

Staff

Clinical and Laboratory Standards Institute
Wayne, Pennsylvania, USA

Luann Ochs, MS
Senior Vice President – Operations
Staff Liaison

Ron S. Quicho, MS
Project Manager

Megan L. Tertel, MA
Editorial Manager

Joanne P. Christopher, MA
Editor

Patrice E. Polgar
Editor

Acknowledgment

CLSI and the Consensus Committee on Evaluation Protocols gratefully acknowledge the following individuals for their help in preparing this document:

A. Paul Durham
APD Consulting
Culver City, California, USA

Jonathan Guy Middle, PhD
Birmingham, United Kingdom

James F. Pierson-Perry
Siemens Healthcare Diagnostics, Inc.
Newark, Delaware, USA

Contents

Contents (Continued)

Foreword

Before a laboratory can introduce a new measurement procedure for reporting results of patient testing, it must evaluate the procedure's analytical performance. Typically, laboratories specify the performance required of the procedure and then verify that the procedure's performance meets the specification. Performance requirements may be defined by regulatory requirements and/or medical usefulness requirements.

In this edition of EP15, the user is **verifying** the manufacturer's claim for precision, and **estimating** bias, because there is unlikely to be a bias claim to verify. The document development committee felt that it was necessary to keep precision and trueness together in one document because the document demonstrates how to measure both in the same experiment.

Most manufacturers follow CLSI document EP05[1] to establish precision claims, and these claims are relatively easily verifiable using the approach prescribed in EP15. The committee chose to keep the number of days in the experiment at five, and to increase the number of replicates per day to five, in order to obtain more reliable estimates of repeatability and within-laboratory imprecision. The most complicated calculations were replaced by tables to make calculations easier and to reduce the opportunities for mathematical errors.

This document is primarily intended for use when an established measurement procedure is initially set up in the laboratory. It may also be used to verify performance after corrective action following a failed proficiency testing event.

NOTE:

Due to the complex nature of the calculations in this guideline, it is recommended that the user have access to a computer and statistical software, such as StatisPro™[2] method evaluation software from CLSI.

KEY WORDS

Bias

Imprecision

Repeatability

Trueness

Verification of performance

Within-laboratory imprecision

NOTE:

Instead of manual worksheets, calculations may be readily performed with **CLSI's StatisPro[2] software** or generic spreadsheet software.

IMPORTANT NOTE:

In any case, the user must follow the protocol described **as closely as possible** in order to obtain reliable results.

Overview of Changes

In this revision of EP15, the experiment to demonstrate trueness using materials with known concentrations was expanded to five days, with encouragement to work with the same sample materials used in the precision verification experiment. The intention of the document development committee was for the user to perform a single experiment to verify precision and trueness simultaneously. This experiment is designed to produce reliable estimates of bias between the mean measurand concentration observed by use of the candidate measurement procedure and the assigned measurand concentration of the material. The degree to which the observed bias is a measurement of trueness depends on the quality of the measurement procedure used to assign the measurand concentrations of the material. As with the precision experiment, complicated calculations were replaced by tables wherever possible.

Similar to previous editions of the document, the document development committee had two principal goals during the development of EP15. One goal was to develop a testing protocol that is suitable for use in the large clinical laboratory, yet simple enough to be applicable in the point-of-care or physician's office laboratory. The second goal was to develop a protocol that is sufficiently rigorous to provide statistically valid conclusions for verification studies. The bias is assessed by a recovery experiment. Instead of manual worksheets, calculations may be readily performed with CLSI's StatisPro[2] software or generic spreadsheet software (see recommendation below).

The committee feels that it is important to provide the interested user with an explanation of the statistical procedures that are used in the document. If the user has access to software specifically designed to perform the calculations described in the document, such as StatisPro,[2] a detailed understanding of the statistics is not necessary. Flow charts are included to provide the user with the necessary overview of the experiment and data processing. In any case, the user must follow the protocol described as closely as possible in order to obtain reliable results.

Chapter 1

Introduction

This chapter includes:

- Document scope and applicable exclusions
- Background information pertinent to the document content
- Standard Precautions information, as applicable
- Terms and definitions used in the document
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions, where applicable
- Abbreviations and acronyms used in the document

User Verification of Precision and Estimation of Bias; Approved Guideline—Third Edition

IMPORTANT NOTE:

This document is **not** intended to establish or validate the precision performance of a measurement procedure.

NOTE:

Because this document's scope is limited to verification of precision and estimation of bias, other more rigorous CLSI protocols (eg, see CLSI documents EP06,[3] EP17,[4] and EP28[5]) are employed to validate the measurement procedure's performance against the user's needs. **CLSI documents EP05[1] and EP09[6] were developed to assist manufacturers in establishing the performance of a diagnostic device for precision and trueness, respectively.** (Also, see CLSI documents EP06,[3] EP17,[4] EP28,[5] and EP10.[7]) CLSI document EP10[7] is intended for the rapid preliminary evaluation of precision, bias, sample carryover, drift, and nonlinearity.

1 Introduction

1.1 Scope

This guideline was developed as a protocol for simultaneously verifying a manufacturer's claims for precision of a measurement procedure and the trueness of the measurement procedure relative to the assigned values of materials with known concentrations.

The precision verification section of the guideline was developed for situations in which the performance of the procedure has been previously established and documented by experimental protocols with larger scope and duration. It has relatively weak power to reject precision claims with statistical confidence, and should only be used to verify that the procedure is operating in accordance with the manufacturer's claims. This document is **not** intended to establish or validate the precision performance of a measurement procedure.

The bias estimation section of the guideline relies on 25 or more measurements by the candidate procedure, made over five or more days, to estimate the measurand concentrations of materials with known concentrations. These estimated measurand concentrations are compared to the assigned measurand concentrations of the materials to estimate bias. The observed bias is a measure of trueness if a high-quality measurement procedure was used to assign the concentrations of the materials.

Because this document's scope is limited to verification of precision and estimation of bias, other more rigorous CLSI protocols (eg, see CLSI documents EP06,[3] EP17,[4] and EP28[5]) are employed to validate the measurement procedure's performance against the user's needs. CLSI documents EP05[1] and EP09[6] were developed to assist manufacturers in establishing the performance of a diagnostic device for precision and trueness, respectively. (Also, see CLSI documents EP06,[3] EP17,[4] EP28,[5] and EP10.[7]) CLSI document EP10[7] is intended for the rapid preliminary evaluation of precision, bias, sample carryover, drift, and nonlinearity.

One may also note that the EP15 protocol has an implicit assumption: Namely, that if the estimated precision and bias are acceptable, then the overall error (eg, total analytical error) of the measurement procedure is acceptable. This implied model can lead to an underestimation of the total analytical error[8] in cases in which other effects are important. Besides conducting more extensive evaluations mentioned above, one could also consider performing the protocol within CLSI document EP21.[9] This protocol is a direct estimation of total analytical error, and does not rely on a model.

1.2 Background

This guideline was written to assist the laboratory in verifying an established measurement procedure. This guideline provides a minimum implementation protocol to verify that a particular example of a procedure is operating in accordance with the manufacturer's claims. The laboratory must test the procedure against these targets for the protocols in this guideline to be applicable.

This guideline can also be used as a protocol to demonstrate acceptable performance when corrective actions are taken, eg, after failing proficiency testing/external quality assessment (PT/EQA).

The specific characteristics (quantities) addressed in this document are repeatability, within-laboratory imprecision, and bias relative to an accepted value. Upon successful completion of the protocols recommended in this guideline, the laboratory will have verified that the procedure is operating in accordance with the manufacturer claims for precision, and can compare the estimated bias relative to materials with known concentration to a specified allowable bias.

This document leads the user through the process of determining the match between the laboratory's actual performance and the expected performance of the procedure. If the laboratory's performance is not consistent with the expected level of performance, remedial actions may be required.

Underlying this protocol is an assumption that the laboratory can operate the procedure properly.

IMPORTANT NOTE:

This guideline can also be used as a **protocol to demonstrate acceptable performance when corrective actions are taken,** eg, after failing proficiency testing/external quality assessment (PT/EQA).

1.3 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to "standard precautions." Standard precautions are guidelines that combine the major feature of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of all known infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of bloodborne pathogens. The Centers for Disease Control and Prevention address this topic in published guidelines that address the daily operations of diagnostic medicine in human and animal medicine while encouraging a culture of safety in the laboratory.[10] For specific precautions for preventing the laboratory transmission of all known infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all known infectious diseases, refer to CLSI document M29.[11]

NOTE:

Underlying this protocol is an assumption that the **laboratory can operate the procedure properly.**

1.4 Terminology

1.4.1 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, International Organization for Standardization (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.

1.4.2 Definitions

analyte – component represented in the name of a measurable quantity (ISO 17511)[12]; **NOTE 1:** In the type of quantity "mass of protein in 24-hour urine," "protein" is the analyte. In "amount of substance of glucose in plasma," "glucose" is the analyte. In both cases, the long phrase represents the measurand (ISO 17511)[12]; **NOTE 2:** In the type of quantity "catalytic concentration of lactate dehydrogenase isoenzyme 1 in plasma," "lactate dehydrogenase isoenzyme 1" is the analyte. The long phrase designates the measurand (ISO 18153)[13]; **NOTE 3:** This includes any element, ion, compound, substance, factor, infectious agent, cell, organelle, activity (enzymatic, hormonal, or immunological), or property, the presence or absence, concentration, activity, intensity, or other characteristics of which are to be determined.

bias (of measurement) – estimate of a systematic measurement error (JCGM 200:2012).[14]

conventional quantity value – quantity value attributed by agreement to a quantity for a given purpose (JCGM 200:2012)[14]; **NOTE 1:** Sometimes a conventional quantity value is an estimate of a true quantity value (JCGM 200:2012)[14]; **NOTE 2:** A conventional quantity value is generally accepted as being associated with a suitably small measurement uncertainty, which might be zero (JCGM 200:2012).[14]

intermediate precision conditions – conditions where test results or measurement results are obtained with the same measurement procedure, on identical test/measurement items in the same test or measurement facility, under some different operating conditions (modified from ISO 3534-2)[15]; **NOTE:** There are four elements to the operating conditions: time, calibration, operator, and equipment (ISO 3534-2).[15]

measurand – quantity intended to be measured (JCGM 200:2012)[14]; **NOTE:** 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 (JCGM 200:2012).[14]

measurement method//method of measurement – generic description of a logical organization of operations used in a measurement (JCGM 200:2012)[14]; **NOTE:** Measurement methods may be qualified in various ways such as substitution measurement method, differential measurement method, and null measurement method; or direct measurement method, and indirect measurement method (see IEC 60050-300:2001)[16] (JCGM 200:2012).[14]

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 (JCGM 200:2012)[14]; **NOTE:** A measurement procedure is usually documented in sufficient detail to enable an operator to perform a measurement (JCGM 200:2012).[14]

measuring 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 measurement uncertainty, under defined conditions (JCGM 200:2012)[14]; **NOTE 1:** In some fields, the term is "measuring range" or "measurement range" (JCGM 200:2012)[14]; **NOTE 2:** The interval (or range) of values (in units appropriate for the analyte [measurand]) over which the acceptability criteria for the measurement procedure have been met; that is, where errors due to nonlinearity, imprecision, or other sources are within defined limits; **NOTE 3:** Formerly, the term "reportable range" was used in EP15, and another commonly used term is "analytical measurement range."

peer group – in proficiency testing, a group of presumably identical test systems.

precision (of measurement) – closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions (JCGM 200:2012)[14]; **NOTE:** Precision is not typically represented as a numerical value but is expressed quantitatively in terms of imprecision—the standard deviation or the coefficient of variation of the results in a set of replicate measurements.

repeatability (measurement) – measurement precision under a set of repeatability conditions of measurement (JCGM 200:2012)[14]; **NOTE:** Formerly, the term **within-run precision** was used in EP15.

repeatability condition (of measurement) – 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 200:2012).[14]

replicate – ***(v)*** to perform a measurement procedure more than once under repeatability conditions using the same or a similar starting test sample; ***(n)*** a value resulting from repeat independent analysis of the same or a similar starting test sample by a measurement process under repeatability conditions; **NOTE 1:** Unless otherwise defined by the manufacturer, the starting point for the measurement process is assumed to follow specimen acquisition and generic processing (eg, centrifugation) and before the start of measurand-specific processing steps in the measurement procedure; **NOTE 2:** Replicates are obtained by processing each starting test sample in a separate sample cup or equivalent (ie, one test result per sample cup).

run – an interval within which the accuracy and precision of a testing system are expected to be stable, but cannot be greater than 24 hours or less than the frequency recommended by the manufacturer; **NOTE 1:** ISO defines "run" as follows: In a series of observations of a qualitative characteristic, the occurrence of an uninterrupted series of the same attribute is called a "run"; **NOTE 2:** Between analytical runs, events may occur that render the measurement process susceptible to important variations.

target value (TV) – the assigned measurand content for a material to which a laboratory should compare its own measurement results; **NOTE:** Depending on the particular material, the TV may be assigned by a reference material manufacturer or from the results of a multilaboratory study.

total error – the sum of any set of defined errors that can affect the accuracy of an analytical result; **NOTE:** This document defines total error as the combination of bias and imprecision.

trueness (of measurement) – closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value (JCGM 200:2012)[14]; **NOTE:** The measure of trueness is usually expressed in terms of bias (ISO 5725-1).[17]

within-device precision//within-run precision – see **intermediate precision conditions.**

within-laboratory imprecision – imprecision over a defined time and operators, within the same facility and using the same equipment. Calibration and reagents may vary; **NOTE:** Formerly, the term "total precision" was used in EP15.

1.4.3 Abbreviations and Acronyms

ANOVA analysis of variance

CEN Comité Européen de Normalisation (European Committee for Standardization)

CI confidence interval

%CV coefficient of variation expressed as a percentage

$\%CV_B$ between-day standard deviation expressed as percentage of the mean

$\%CV_R$ repeatability standard deviation expressed as percentage of the mean

$\%CV_{WL}$ within-laboratory standard deviation expressed as percentage of the mean

DF degrees of freedom

df_C combined degrees of freedom

df_R degrees of freedom for repeatability

df_{RM} degrees of freedom for reference materials

df_{WL} degrees of freedom for within-laboratory imprecision

EQA external quality assessment

IS International Standard(s)

ISO International Organization for Standardization

JCTLM Joint Committee for Traceability in Laboratory Medicine

MS mean squares

nSam number of samples

NIST National Institute of Standards and Technology

PI package insert

PT proficiency testing

QC quality control

σ_R manufacturer's claim for repeatability

σ_{WL} manufacturer's claim for within-laboratory imprecision

SD standard deviation

SI Système International d'Unités (International System of Units)

S_R user estimate for repeatability

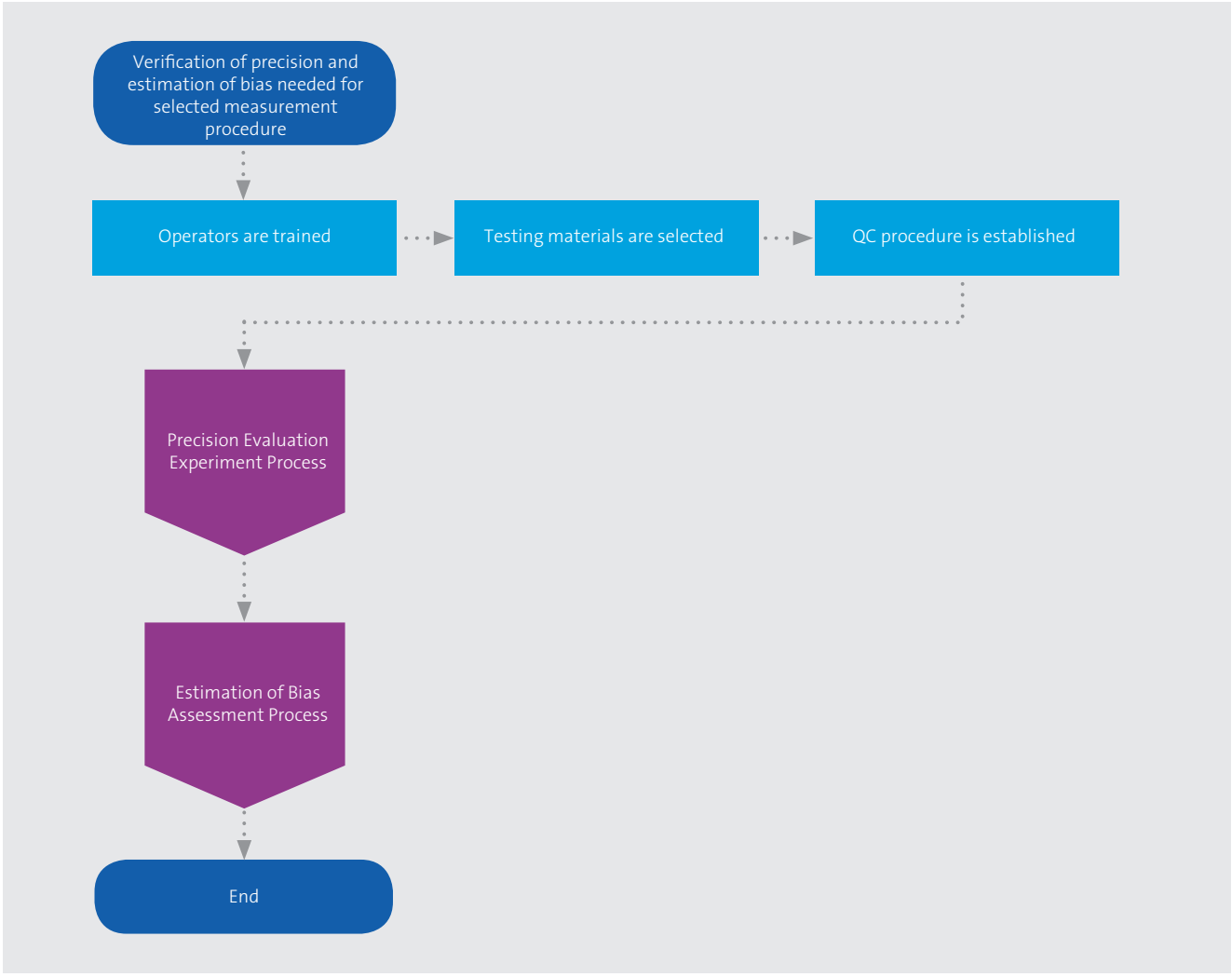
SS sum of squares

S_{WL} user estimate for within-laboratory imprecision

TV	target value
UVL	upper verification limit
V_B	variance between runs
V_W	variance within run
WHO	World Health Organization

1.5 Overview of the Protocol

The EP15 protocols for precision verification and demonstration of trueness involve repeated measurement of samples over five working days. With proper planning and judicious choice of samples, the bench work can be completed in a single week, though additional days are recommended when greater reliability is important. If samples with known concentrations are used for the precision experiment, results from a single experiment can be analyzed for bias (a measure of trueness) as well as for precision. Figure 1 shows a basic overview of the process involved in precision evaluation and estimation of bias.



Abbreviation: QC, quality control.

Figure 1. Process Flow Chart for Precision Evaluation and Estimation of Bias Assessment

1.5.1 Device Familiarization Period (see Section 2.1)

The device familiarization period is the time given to operators to become both familiar and comfortable with the details of the instrument's operation and the measurement procedure. Including a familiarization period into the timeline for an evaluation study is critical for meaningful evaluations of precision. If the operator has not had the opportunity for a familiarization period, including the opportunity to perform the measurement before beginning the precision protocol, the first data points generated by the operator may cause the laboratory to assume the test system has a higher level of imprecision and bias than is actually the case.

The familiarization period is also the time to verify that the QC materials the laboratory intends to use for the procedure perform as expected.

IMPORTANT NOTE:

Including a familiarization period into the timeline for an evaluation study is **critical for meaningful evaluations of precision.**

IMPORTANT NOTE:

Lists of medically based performance standards are **provided in the references.[18,19]**

1.6 Performance Standards

Before selecting a specific procedure for measuring the concentration of an analyte and evaluating that procedure's performance, the laboratory must establish minimum performance specifications based on the clinical needs of the laboratory's clients. Lists of medically based performance standards are provided in the references.[18,19] Some regulatory and accreditation programs[a] specify minimum standards for performance in PT. If regulatory performance standards apply, these standards define the maximum allowable measurement error the measurement procedure may deliver. These standards are expressed in terms of total allowable difference (total error) from an accepted target value (TV). Discussions of the relationship between allowable error and allowable imprecision and bias are included in the references.[15,16] The user can also refer to CLSI document EP21.[9]

For the performance characteristics evaluated in this document, the following performance goal formats are recommended in order to conform to the evaluation result formats:

Precision. Precision goals should be stated as the maximum allowable imprecision, SD, and/or CV expressed as a percentage (%CV) at each analyte concentration to be tested. Where appropriate, the user compares the manufacturer claims to these performance goals. Ideally, the laboratory can select a measurement procedure whose manufacturer claims for imprecision are within the limits of the performance specifications of the laboratory. If the manufacturer's imprecision claims exceed the specified imprecisions, the user should not attempt to verify the imprecision claims. The user has the choice of selecting another candidate procedure, or relaxing the specification in the situation in which no measurement procedure meets the specification.

Trueness (bias). Trueness goals for bias should be stated as the maximum allowable bias, at each analyte concentration to be tested, that is not exceeded with certain probability. Maximum allowable bias may be expressed in either absolute or relative terms—that is, either as a deviation, in concentration units, or as a percent deviation, as either an absolute concentration or as a percentage of the concentration.

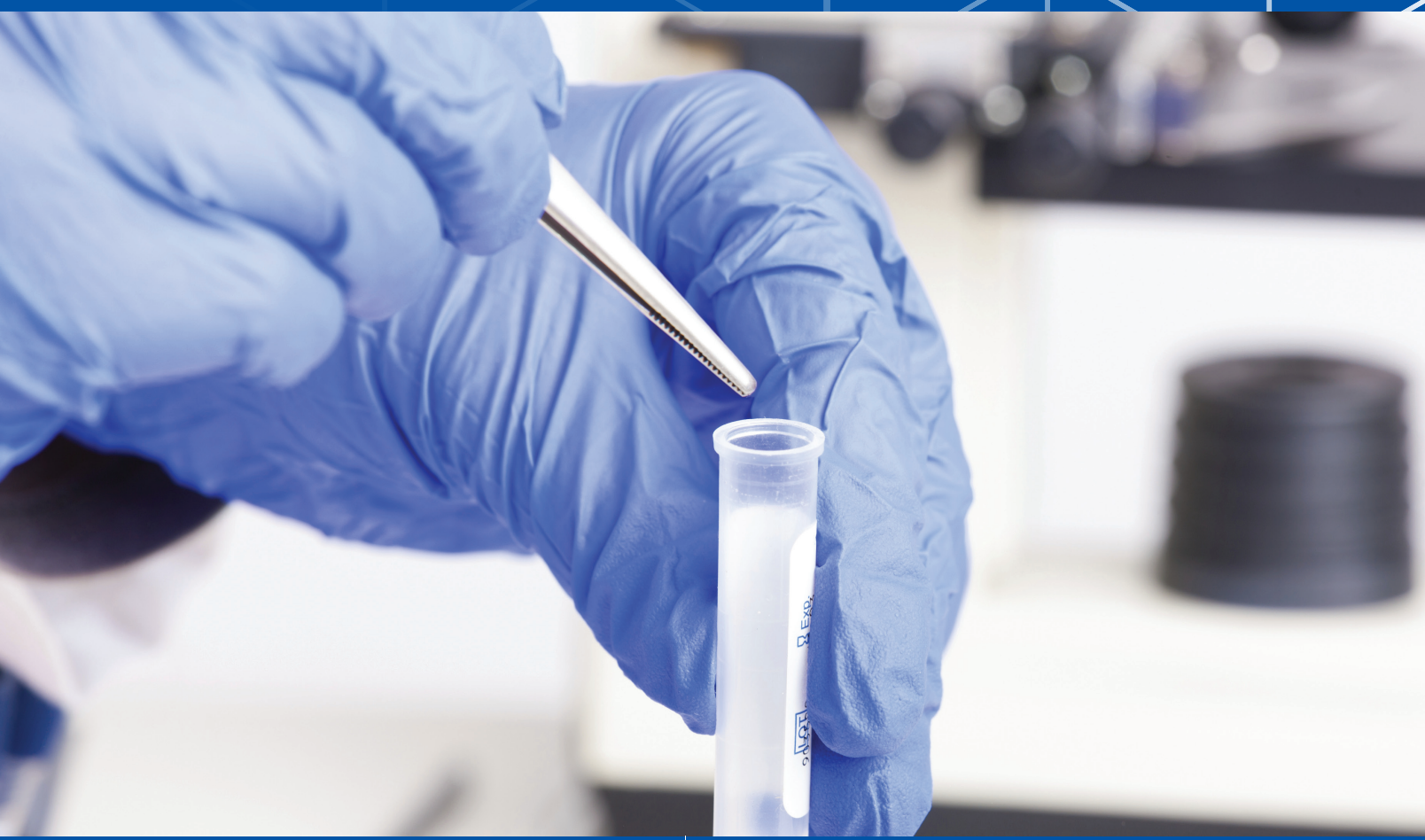
[a] For example, in the United States, the Clinical Laboratory Improvement Amendments and the College of American Pathologists.

Chapter 2

Precision Verification Study

This chapter includes:

- General guidance on operator training and QC procedures
- Overview and limitations of the precision verification study
- Experimental procedure designs



2 Precision Verification Study

2.1 Familiarization Period

After the system has been inspected by the manufacturer, staff must become familiar with the operation, maintenance procedures, methods of sample preparation, calibration, and monitoring functions. The length of time required for this process is variable, depending on the complexity of the device. If appropriate, calibration should be verified during this period (see CLSI document EP06[3]). At the end of this period, the operator(s) should be confident in the operation of the device.

2.1.1 Operator Training

The operation, maintenance procedures, methods of sample preparation, and calibration and monitoring functions must be learned. Some manufacturers provide this training. The device should be set up and operated in the individual laboratory long enough for operators to understand all of the procedures involved in order to avoid problems during the evaluation of its performance. Training should include the use of actual sample material, including pools, controls, leftover patient samples, or any other test materials appropriate for the device.

IMPORTANT NOTE:

Training should include the use of actual sample material, including pools, controls, leftover patient samples, or any other test materials appropriate for the device.

All possible contingencies (eg, error flags, error correction, calibration) that may arise during routine operation should be carefully monitored. Data should not be collected during this period. Operator training is not complete until the user can confidently operate the device (see CLSI document QMS03[20]).

IMPORTANT NOTE:

Data should not be collected during the familiarization period. Operator training is not complete until the user can confidently operate the device (see CLSI document QMS03[20]).

2.1.2 Quality Control Procedures

QC procedures to be followed during the protocol are established during the familiarization period. It is important to verify that the device is operating in control, according to the manufacturer's specifications. To demonstrate this fact, use the control procedures recommended by the manufacturer. Due to the short duration of this protocol, the estimated SDs should not be used by themselves to establish QC limits. For guidance on establishing ongoing QC procedures, refer to CLSI document C24.[21]

NOTE:

For guidance on establishing ongoing QC procedures, refer to CLSI document C24.[21]

2.1.3 Documenting the Studies

Follow good documentation practices. Ensure traceability of the data analyses and conclusions to the experimental testing and manufacturer claims along with observations, interpretations, and troubleshooting. Documentation should address the **study** as a whole, and also at the individual sample **run** and **replicate** levels.

It is important to record:

- The device name and measurand information (analyte, kind of quantity, and units)
- Reagent and calibrator lot numbers
- Justification for selecting the concentrations tested
- The composition of the samples and, if known, their TVs and uncertainties
- The source of the precision claims (usually a table in the manufacturer's package insert [PI]) and the value assignments for the known concentration used for demonstrating trueness
- The software tools used and their version numbers
- The persons responsible for testing, data review, and data processing
- The experimental design and any decisions as to its extension

The laboratory director should sign off on the precision verification and trueness studies, including assessments of the statistical results in light of manufacturer claims and allowable limits, and decisions regarding the subsequent role of the assay in the laboratory's operations.

2.1.4 Data Processing Strategy

When deciding on a data processing strategy, several potential sources of error should be kept in mind:

- Assembly of the raw data is not the sole error source. Every reformatting to produce input for a calculation step carries the risk of transcription errors, and creates the need for additional proofreading.
- Manual tabulation of intermediate results entails either a risk of accumulating round-off error or an increased proofreading burden, depending on whether the number of digits retained is small or large, respectively.
- When working with spreadsheet applications, special attention should be paid to worksheet integrity and the correctness of cell formulae.
- Both built-in functions and external software are associated with input and output issues. Data and parameters must be submitted in the proper order and format. When output is verbose, as is true for typical analysis of variance (ANOVA) routines, the relevant elements must be identified and extracted.

NOTE:

The **precision verification study described** in this document has three parts:

- Repeated measurements over five days
- Calculations of repeatability and within-laboratory precision estimates
- Assessment of consistency of estimates with the claims

NOTE:

Uses of a precision verification study:

- Assess consistency of observed assay precision performance vs pre-established claims before introducing assay into routine use.
- Assess precision performance as part of a corrective action plan following a PT failure.
- Assess precision during assay optimization studies.
- Use as part of instrument or assay troubleshooting efforts.

Accordingly, the calculations are presented wherever possible in the form of look-up tables or in relatively simple algebraic form, avoiding the use of matrix notation. This presentation is meant to facilitate 1) implementing and verifying routines in a programming language or generic spreadsheet environment, and/or 2) confirming the suitability of off-the-shelf software routines. It is strongly recommended that users test their software against the numerical examples provided in order to spot check the software's fitness for use in this context. (The examples supplied are too limited to serve as a basis for validating the software routines.)

2.2 Overview and Limitations of the Precision Verification Study

The precision verification study described in this document is a small experiment, involving repeated measurements of two or more samples over (at least) five days, calculation of repeatability and within-laboratory imprecision estimates, and assessment of their consistency with the claims. It is primarily intended for use by laboratorians to assess consistency of observed measurement procedure imprecision performance vs pre-established claims before introducing the assay into routine use. However, the study may be used for other purposes, such as assessing precision performance as part of a corrective action plan following a PT failure, assessment of precision during assay optimization studies, or as a part of instrument or troubleshooting efforts, among other applications.

The study design represents a compromise between costs to the user associated with time and materials, and the risk of an inadequate or misleading assessment of the procedure's precision. While estimates of repeatability and within-laboratory imprecision could be generated through separate experiments, the integrated (single experiment) approach recommended in this document offers significant advantages in terms of efficiency, computational rigor, and robustness of the repeatability estimates.

This section describes a process for verifying precision claims made by a manufacturer for a measurement procedure, which could be either a commercially developed procedure or a laboratory-developed test. For a commercially developed procedure, such claims typically are presented within the assay's PI as a table of experimentally determined repeatability and within-laboratory imprecision estimates, expressed as SDs and/or as %CVs, at several measurand concentrations.

"Repeatability" refers to variability due solely to within-run (within-batch) factors. It reflects inherent variability over a **short** period of time under conditions minimizing other sources of variation. "Within-laboratory imprecision" (or "within-device imprecision")—also referred to by the outdated term "total precision" in some PIs—refers to variability due to run-to-run and day-to-day factors **in addition to** repeatability sources.

Accordingly, at any given measurand concentration, a procedure's within-laboratory imprecision usually exceeds repeatability and cannot be less.

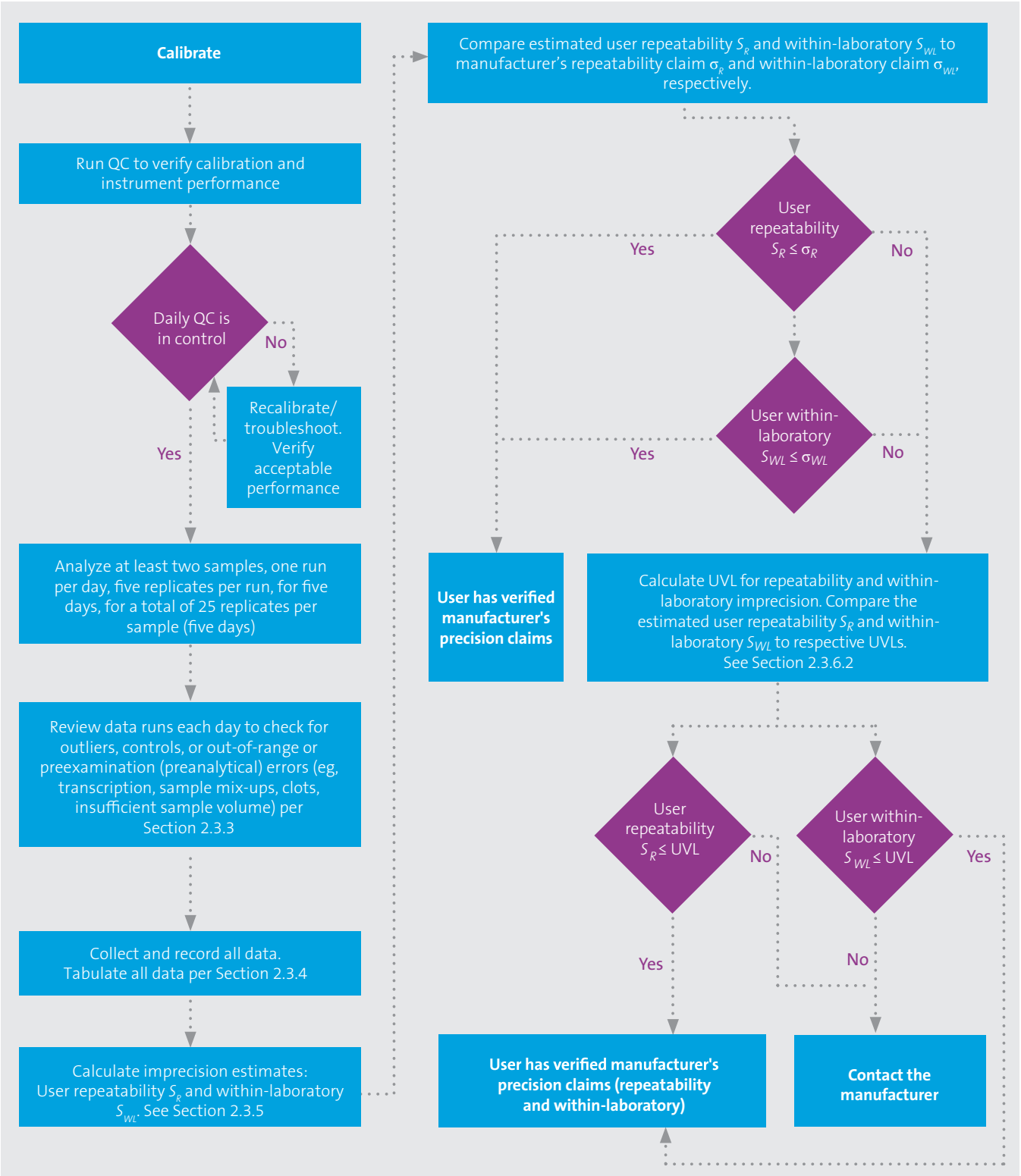
To distinguish between SD **claims,** which come from the manufacturer (or developer) and are treated as if they were known without uncertainty, and SD **estimates,** which are calculated from the user's verification testing results, this document uses Greek and Roman letters respectively, appropriately subscripted to indicate the precision type, as shown in Table 1.

Table 1. Nomenclature of Precision Terms

Precision Type	Manufacturer Claim	User Estimate
Repeatability	σ_R	s_R
Within-laboratory imprecision	σ_{WL}	s_{WL}

2.2.1 Precision Evaluation Experiment

The precision evaluation experiment provides the user with guideline procedures for demonstrating precision performance. Usually, the manufacturer makes two types of precision claims—repeatability (within-run imprecision) (σ_R) and within-laboratory imprecision (σ_{WL}). This section provides statistical methods for identifying gross deviations from both types of claims. Some of the calculations described in the precision verification section are also relevant to the subsequent analysis of relative bias. Figure 2 depicts a flow chart of the precision evaluation experiment.



Abbreviations: σ_R, manufacturer's claim for repeatability; σ_{WL}, manufacturer's claim for within-laboratory imprecision; s_R, user estimate for repeatability; s_{WL}, user estimate for within-laboratory imprecision; QC, quality control; UVL, upper verification limit.

Figure 2. Overview of Verification and Imprecision Estimates (Repeatability and Within-Laboratory) for Each Test Sample in the Study

The experimental design and data analyses are similar to those described in CLSI document EP05,[1] which is regularly used by manufacturers to establish precision claims. In particular, both studies use ANOVA to calculate estimates of imprecision from multiday studies.

The amount of testing for EP15 is substantially reduced compared to that in CLSI document EP05,[1] in order to be practical for end users. Because of the substantially reduced amount of testing, however, and because the EP15 consistency check is designed to protect the user from failing more than approximately 5% of the time simply due to chance, discrepancies between manufacturer claims and user observed precision performance will not be **reliably** flagged unless they are quite large.

REMINDER:

CLSI's StatisPro[2] software provides a complete, user-friendly implementation of the EP15 data analysis, but this can also be handled by combining readily available ANOVA software with table look-ups and simple spreadsheet calculations.

2.3 Experimental Procedure Design

The precision verification study calls for repeatedly testing **at least** two samples with different measurand concentrations. The basic 5 × 5 design—five days, one run per day, five replicates per run—should yield a total of 25 results per sample.

To improve the rigor of the estimates, the experiment could be extended to include additional runs, preferably on additional days, for any one or more of the samples. Alternatively, for example, just four replicates could be tested for each sample on each one of seven days, in order to obtain a somewhat more reliable within-laboratory imprecision estimate, without compromising the repeatability estimate.

Judicious design modifications of this nature are acceptable, and the calculations described in this guideline can accommodate them. In no case, however, may a design use less than five days per sample. Note, however, that five replicates must be tested in each run if the same samples and experiment are used to estimate imprecision and bias, and the experimenter will use Tables 15A, 15B, and 15C of Section 3.5, because the tables support five, six, and seven runs of five replicates each, respectively (no fewer replicates).

The operational definition of a "run" for the verification study should follow what the manufacturer did in establishing the claims. Most commonly, this means processing all replicates contiguously for a given sample and day, ie, in the shortest possible time period. Alternative approaches could involve processing the replicates distributed over an eight-hour shift or other time period, depending on how the manufacturer defines a run for its precision study.

IMPORTANT NOTE:

Selecting samples with levels close to those reported in the PI may greatly simplify identifying the claims relevant to the final consistency checks. In any case, **avoid extreme levels** that would require extrapolating beyond the interval spanned by the PI levels or that **might yield results outside the measuring interval for some replicates.**

NOTE:

Sample processing days need not be consecutive calendar days, nor is it essential that all samples be processed in the same runs or even on the same days.

IMPORTANT NOTE:

Do not simply preprocess a sample or aliquot once and then perform replicate analyses on it. Perform the preprocessing as was done by the manufacturer to establish the precision claims.

2.3.1 Samples

Select **at least** two samples for the study, preferably individual patient samples, pools thereof, or commercial QC materials consistent with those used by the manufacturer to establish the precision claims.

The samples should have different measurand concentrations, preferably ones that represent clinical decision points (cutoffs) or reference limits, or simply fall in normal and abnormal regions. If the goal is to verify manufacturer claims across all or most of the procedure's stated measuring interval, optimal choices for the number of samples and their concentration levels will depend on how imprecision varies across that interval. Selecting samples with levels close to those reported in the PI may greatly simplify identifying the claims relevant to the final consistency checks. In any case, avoid extreme levels that would require extrapolating beyond the interval spanned by the PI levels, or that might yield results outside the measuring interval for some replicates.

Samples should be prepared and stored in order to ensure their stability throughout the study. A common practice is to aliquot and freeze the samples, providing this is appropriate for the measurand. In deciding on the size and number of the aliquots, be sure to allow for "dead volumes" and the possibility that additional runs may be needed.

2.3.2 Processing

At the beginning of the study, calibrate the procedure according to the manufacturer's instructions. If the precision claims were generated during multiple calibration cycles, consider incorporating additional calibration events during the study.

Schedule daily work assignments so that testing is representative across operators. This consideration is important even for fully automated procedures, which may be affected by operator-related sources of variation, such as sample handling.

For each sample, process five replicates in a single run, on each of five or more days. These need not be consecutive calendar days, nor is it essential that all samples be processed in the same runs or even on the same days. In each run, include QC materials with predetermined criteria for accepting or rejecting the run, if they are available.

For procedures that require sample processing before analysis (eg, extraction or dilution), ensure that each replicate undergoes all steps in the procedure, ie, the preprocessing as well as the subsequent analysis. Do not simply preprocess a sample or aliquot once and then perform replicate analyses on it. Perform the preprocessing as was done by the manufacturer to establish the precision claims.

2.3.3 Data Integrity

Examine all results each testing day—double-checking the entry of extreme results—in order to identify errors not reflective of expected assay performance. If an entire run is flagged as bad by the assay system, or if it is rejected by the internal QC criteria, discard all results for that run. After correcting for transcription errors, clear-cut sample mix-ups, and the like, exclude any other results determined, ie, **known,** to have arisen from **nonperformance-related** errors, such as the presence of clots, system processing errors, insufficient sample volume, etc. Do not rely on presumption or speculation, and do not reject or repeat results merely because they seem aberrant. Carefully document the circumstances and reasons for the corrections, exclusions, missing values, and repeats, accounting for all runs and all replicates.

If the new results can be considered part of the same "run," individual results identified as missing or erroneous may immediately be repeated. Otherwise, schedule additional runs as needed in order to ensure that the overall minimal requirements for the final dataset are met or exceeded. For each sample, there must be results from at least five runs and the total number of individual results minus the number of runs must be no less than 18, but preferably 19 or more. Decisions to extend the duration of the study may be made even after the study is started.

IMPORTANT NOTE:

Do not rely on presumption or speculation, and do not reject or repeat results merely because they seem aberrant. Carefully document the circumstances and reasons for the corrections, exclusions, missing values, and repeats, accounting for all runs and all replicates.

2.3.4 Data Analysis for Individual Samples

NOTE: This section assumes that the user's experiment conforms to the basic 5 × 5 design, with possibly one or two additional runs, and that the calculations are being performed using one-way ANOVA software. For other designs, consult Appendix B, and/or use comprehensive statistical software such as CLSI's StatisPro.[2]

Once the experimental work is completed and checked for data integrity, analyze the results for each sample as follows:

- Tabulate the results.
- Inspect the results for discordant values; if discordant values are found, test for outliers.
- Calculate estimates for repeatability and within-laboratory imprecision.
- Compare these estimates to their corresponding precision claims.

Tabulation and Inspection of Results

The best way to tabulate the dataset for each sample can depend in part on the input format expected by the ANOVA software. Table 2 (left table) shows one way to list the data. The results are from the ferritin worked example in Section 2.3.10, which follows the basic 5 × 5 design.

Table 2. Ferritin Example: Raw Data Listing (Left); Simple Tally, by Run (Right)

µg/L	Run 1	Run 2	Run 3	Run 4	Run 5
Rep 1	140	140	140	141	139
Rep 2	139	143	138	144	140
Rep 3	138	141	136	142	141
Rep 4	138	143	141	143	138
Rep 5	140	137	136	144	141

Abbreviation: rep, replicate.

µg/L	Run 1	Run 2	Run 3	Run 4	Run 5
136			X X		
137		X			
138	X X		X		X
139	X				X
140	X X	X	X		X
141		X	X	X	X X
142				X	
143		X X		X	
144				X X	

Inspection of the raw data listing shows no missing values. The dataset is said to be **balanced,** because every run has the same number of results. If the number of results per run was varied due to missing values or results suppressed as statistical outliers, the dataset would be said to be **unbalanced.**

It is useful to visualize the distribution of results in order to inspect for individual values or entire runs that are highly discordant relative to the bulk of the data. Table 2 (right table) illustrates one of many ways to visualize this distribution: a simple manual tally. Other approaches such as plots or simple sorted lists may be more readily implemented with a spreadsheet. For this example, the tally in Table 2 (right table) shows no apparent outliers and reasonable consistency from run to run in the scatter of values.

After correcting typographical errors and the like, proceed directly to the calculations to estimate imprecision (see Section 2.3.5) with all *bona fide* data available, skipping the discussion of formal outlier tests (see Section 2.3.4.1). At this stage, do not remove any measurements as statistical outliers from the analysis; an analysis based on all the data, with no points excluded, will be required in any case. If the precision verification test passes, no outlier-related calculations will be necessary. If the precision verification test fails, and the dataset includes a highly discordant measurement, then apply the formal test described in Section 2.3.4.1. If, and only if, the measurement qualifies as an outlier by that test, repeat the calculations in order to estimate imprecision, omitting the discordant result.

2.3.4.1 Potential Outliers

Even after correcting or excluding all results known to be spurious (see Section 2.3.3), a result may stand out as discordantly high or low. This might be due to a nonperformance-related cause, which, if known, would have justified excluding the result. Alternatively, the apparently extreme result might genuinely represent the assay's measurement procedure performance and would not be so discordant if viewed in the distribution of results from a larger study. The trade-off is that retaining an apparent outlier risks calculating inflated imprecision estimates, while excluding it risks calculating unduly optimistic estimates.

IMPORTANT NOTE:

Retaining an apparent outlier risks calculating inflated imprecision estimates, while excluding it risks calculating unduly optimistic estimates.

This guideline allows for treating such highly discordant results as "statistical outliers" but imposes certain conditions to ensure objectivity:

- At most, one result per sample may be treated as a statistical outlier.
- The result must qualify as an outlier by a suitable test (eg, the Grubbs' test described in Section 2.3.4.2).
- At most, two results may be treated as statistical outliers across all samples in the full study.

When a result is to be treated as a statistical outlier, good practice calls for analyzing the sample's data twice: both before and after excluding the result. If **multiple** outliers are observed—more than one for a given sample, or more than two in the entire study—the user should consider repeating the entire precision verification study and/or contacting the manufacturer for support.

NOTE: Even if a result formally qualifies as a statistical outlier, it does not have to be treated as such if the practical outcome of its presence does not affect the outcome of the verification study. If the suspected outlier must be removed in order for the procedure's imprecision (see discussion of bias in Chapter 3) to be acceptable, it is good practice to perform the calculations with the suspected outlier included, as well as without it. Assess the clinical effect of the suspected outlier, and investigate further to try to determine the cause of the suspected outlier. The handling of any suspected outlier must be documented in the evaluation report for the laboratory director's review.

IMPORTANT NOTE:

The handling of any suspected outlier **must be documented in the evaluation report** for the laboratory director's review.

2.3.4.2 Grubbs' Test for Outliers

Although any suitable test may be used to justify treating a result as a statistical outlier, this guideline recommends a version of the Grubbs' test.[22,23] In this approach, a result qualifies as a statistical outlier **if, and only if,** it lies more than *G* SDs from the sample mean, where:

- The mean and SD are based upon all N results for the sample, including the suspected outlier.
- The Grubbs' factor *G* (which depends on N) comes from Table 3.

Table 3. Grubbs' Factor (*G*) and "Average" Number of Results per Run (n_0) as Functions of the Total Number of Results, N, for Five to Seven Runs, Five Replicates per Run, With up to Two Results Missing. For a larger table of Grubbs' factors, see Section B3 in Appendix B.

5 Runs		
N	*G*	n_0
23	3.087	4.565
24	3.112	4.792
25	3.135	5

6 Runs		
N	*G*	n_0
28	3.199	4.643
29	3.218	4.828
30	3.236	5

7 Runs		
N	*G*	n_0
33	3.286	4.697
34	3.301	4.853
35	3.316	5

While visual inspection of the ferritin data listed in Table 2 (left table) offers no reason to believe that any result might be considered a statistical outlier, the data can be used to illustrate the Grubbs' test. The mean and SD of all results are calculated to be 140.1 and 2.30 µg/L, respectively. As the example comes from a design of five runs, study of Table 3 yields *G* = 3.135 for N = 25. The lower and upper Grubbs' limits are then calculated as:

Grubbs' limits = mean ± *G* • SD = 140.1 ± 3.135 • 2.30 = 132.9 and 147.3 µg/L, respectively.

Because all of the results fall well within these limits, none qualifies as a statistical outlier, as expected, because there was no apparent discordant value.

2.3.5 Imprecision Estimates by One-Way Analysis of Variance

NOTE:

In the absence of dedicated statistical software like CLSI's StatisPro,[2] it is assumed that users will make use of an ANOVA routine.

One-way ANOVA is the basis for calculation of repeatability and within-laboratory imprecision estimates for each sample. In the absence of dedicated statistical software like CLSI's StatisPro,[2] it is assumed that users will make use of an ANOVA routine.

The principal output of a one-way ANOVA routine is a summary table like the ones shown in Tables 4 and 5. While terminology and format may vary depending on the routine used, the basic layout and meaning of the table elements remain the same. The purpose of the ANOVA is to partition the total variability of the dataset for a sample into within-group and between-group fractions. In the context of this guideline, the grouping factor is **runs.**

Table 4. Generalized One-Way ANOVA Summary Table Format

Source of Variation	*SS*	*DF*	*MS*
Between-run	*SS1*	*DF1*	*MS1*
Within-run	*SS2*	*DF2*	*MS2*
Total	SS_{total}	DF_{total}	

Abbreviations: ANOVA, analysis of variance; *DF*, degrees of freedom; DF_{total}, total degrees of freedom; *MS*, mean squares; *SS*, sum of squares; SS_{total}, total sum of squares.

In addition to the table, some ANOVA routines also provide the calculated between-run and within-run variance **components,** namely V_B and V_W. If that information is not provided, calculate V_B and V_W from the ANOVA table values as follows.

$$\text{Set } V_W = MS2. \quad (1)$$

If $MS1 \leq MS2$ (this is comparatively rare), set $V_B = 0$; otherwise:

$$V_B = (MS1 - MS2) / n_0 \quad (2)$$

where n_0 comes from Table 3, based on the number of runs and total number of results for the sample, and represents the "average" number of results per run. For more discussion of the average number of results per run, see Appendix A.

The variance component V_W corresponds directly to repeatability variance, and V_B the "pure" between-run variance, ie, the between-run variance corrected for the contribution of within-run variance, whereas the **sum** of the two variance components (V_W and V_B) corresponds to within-laboratory precision. Taking square roots yields the desired precision estimates expressed as SDs:

$$s_R = \sqrt{V_W} \quad (3)$$

$$s_B = \sqrt{V_B} \quad (4)$$

$$s_{WL} = \sqrt{V_W + V_B} \quad (5)$$

In relative terms, $\%CV_R = s_R \cdot 100/\bar{\bar{x}}$ and $\%CV_{WL} = s_{WL} \cdot 100/\bar{\bar{x}}$, where $\bar{\bar{x}}$ is the grand mean of all results for the sample.

Continuing with the ferritin example data from Table 2 (left table), a one-way ANOVA routine yielded the summary output shown in Table 5.

Table 5. Ferritin Example: ANOVA Table

Source of Variation	*SS*	*DF*	*MS*
Between-run	63.44	4	15.86
Within-run	63.20	20	3.16
Total	126.64	24	

Abbreviations: ANOVA, analysis of variance; *DF*, degrees of freedom; *MS*, mean squares; *SS*, sum of squares.

Based on these table entries, $V_W = MS2 = 3.16$. Because $MS1$ (15.86) > $MS2$ (3.16), V_B is calculated as:

$V_B = (MS1 - MS2) / n_0 = (15.86 - 3.16) / 5.0 = 2.54$, where $n_0 = 5$ comes from Table 3 for a design of five runs with N = 25 total results.

From these variance component values, the desired imprecision estimates in SD units are calculated as:

$$s_R = \sqrt{V_W} = s_R = \sqrt{3.16} = 1.78 \text{ µg/L}$$
$$s_B = \sqrt{V_B} = \sqrt{2.54} = 1.59 \text{ µg/L}$$
$$s_{WL} = \sqrt{V_W + V_B} = s_{WL} = \sqrt{3.16 + 2.54} = 2.39 \text{ µg/L}$$

Expressed in %CV units, based on the grand mean of 140.12 µg/L, these estimates are $\%CV_R = 1.27\%$, $\%CV_B = 1.14\%$, and $\%CV_{WL} = 1.71\%$. In this example, the pure between-run imprecision is s_B less than the within-run imprecision. Estimating and expressing s_R, s_B, and s_{WL} helps the laboratory identify and quantify the sources of uncertainty.

IMPORTANT NOTE:

Estimating and expressing s_R, s_b, and s_{WL} **helps the laboratory identify and quantify the sources of uncertainty.**

2.3.6 Comparison of User Imprecision Estimates to Manufacturer Claims

After calculating the repeatability and within-laboratory imprecision for each sample in the precision verification study, the user must check each of these estimates for consistency with the manufacturer claims for the measurement procedure. If the actual imprecision is, on average, equal to the claimed imprecision, the observed imprecision will be greater than the claimed imprecision 50% of the time due to chance alone.

To limit the rate of failures to verify the manufacturer's claims due to chance alone, a UVL may be calculated for the claim. The UVL represents the upper 95th percentile expected for imprecision estimates obtained in an experiment similar in size and design to the user's precision verification study when the claim is correct. Allowing the imprecision verification acceptance criterion to be the UVL rather than the claim itself protects the user from inappropriately failing solely due to chance more than about 5% of the time.

IMPORTANT NOTE:

Allowing the imprecision verification acceptance criterion to be the UVL rather than the claim itself **protects the user from inappropriately failing solely due to chance more than about 5% of the time.**

For a given sample, the user's repeatability estimate is said to be **consistent** with the manufacturer's claim if, and only if, the estimate is less than or equal to the claim or, failing that, less than or equal to the associated UVL for the claim at the sample's observed measurand concentration. Other terminology in common use is that an estimate meeting this criterion "verifies" the claim or, more briefly, that it "passes." The same assessment applies for the within-laboratory precision estimate relative to its associated claim. Computation of UVLs is described in Section 2.3.6.2.

NOTE:

Computation of UVLs is described in Section 2.3.6.2.

As the UVL always exceeds its associated claim, generally by at least 30%, the user estimate can be somewhat higher than the claim and still pass.

Accordingly, the consistency check can be performed efficiently in two steps:

1. Compare all repeatability and within-laboratory imprecision estimates directly to their respective claims.
2. For any estimate that exceeds its associated claim, calculate the relevant UVLs and compare the estimate to it.

While it is possible to calculate UVLs for all claims (as done for the worked example in Section 2.3.10), that may not always be necessary. Consistency can often be determined by simple inspection, without the need for formal evaluation of either claims or UVLs at the measurand concentration observed for the samples.

2.3.6.1 Identifying the Manufacturer's Precision Claims

This guideline assumes that manufacturer precision claims are **representative,** ie, that they characterize "typical" or "average" (as opposed to "worst case") performance. Such claims are nearly always summarized in the manufacturer's PI as a table of experimentally determined means, SDs, and/or %CVs for repeatability and within-laboratory imprecision at several measurand concentrations. The PI also may include a "precision profile"[24,25] for repeatability and/or within-laboratory imprecision. A precision profile is a curve that graphically depicts how the %CV (or SD) changes as a function of the measurand concentration across the measurement procedure's measuring interval.

In order to check consistency of user imprecision estimates with the manufacturer's claims, it is necessary to identify exactly what the relevant claims should be for the samples used in the precision verification study. It cannot be expected that the mean measurand concentrations ($\bar{\bar{x}}$s) observed for these samples would exactly match those in the PI's imprecision table. Sometimes, for example, the %CVs tabulated for the mean closest to a sample's $\bar{\bar{x}}$ may reasonably be adopted as the manufacturer claims at that concentration. However, it may often be more appropriate to ascertain the claims at $\bar{\bar{x}}$, by interpolation or averaging, from statistics tabulated in the PI for the **two or three** means in the neighborhood of that concentration level. (If the PI provides an imprecision profile, claims at the $\bar{\bar{x}}$s for the imprecision estimate depicted may be read off the curve.)

NOTE:

A precision profile is a curve that graphically depicts how the %CV (or SD) changes as a function of the measurand concentration across the measurement procedure's measuring interval.

2.3.6.2 Performing the Comparisons

If an imprecision estimate does not exceed the corresponding claim, it meets the consistency criterion. The user estimate passes and directly verifies the manufacturer's claims.

If an estimate does exceed the manufacturer's claim, the user should implement the second part of the consistency check and compare the estimate to the corresponding UVL for that claim.

A three-step table look-up approach to calculating UVLs is described as follows.

1. Determine the degrees of freedom, *df,* for the type of imprecision estimate in question (df_R for repeatability or df_{WL} for within-laboratory imprecision).
2. Determine the UVL factor *F* from Table 7.
3. Calculate the UVL from the UVL factor *F* and the manufacturer claim.

Compare estimated imprecision with UVL.

Degrees of Freedom

For a **repeatability** comparison, calculate the degrees of freedom, df_R, directly as $df_R = N - k$, where N is the total number of results and *k* is the number of runs.

For a **within-laboratory imprecision** comparison, first calculate the claims ratio, ρ, rho at the test sample average concentration $\bar{\bar{x}}$ as:

$$\rho = \sigma_{WL} / \sigma_R = \%CV_{WL} / \%CV_R \quad (6)$$

which is the manufacturer's within-laboratory imprecision claim divided by the manufacturer's repeatability claim, either expressed in SD units or in %CV units. Then, determine the approximate degrees of freedom, df_{WL}, from Table 6. Select the column representing the number of runs in the precision verification study for the particular test sample, scan down the table entries to find the ρ value that most closely matches the calculated value, and then read off the associated df_{WL} value.

Table 6. df_{WL} as a Function of the Claims Ratio ($\rho = \sigma_{WL} / \sigma_R$), for Five to Seven Runs, Five Replicates per Run

5 Runs	
ρ	df_{WL}
2.74	5
2.06	6
1.78	7
1.62	8
1.51	9
1.43	10
1.37	11
1.32	12
1.28	13
1.24	14
1.21	15
1.19	16
1.16	17
1.14	18
1.12	19
1.10	20
1.08	21
1.05	22
1.03	23
1.00	24

6 Runs	
ρ	df_{WL}
3.02	6
2.25	7
1.93	8
1.74	9
1.62	10
1.52	11
1.46	12
1.40	13
1.35	14
1.32	15
1.28	16
1.25	17
1.23	18
1.20	19
1.18	20
1.16	21
1.14	22
1.12	23
1.11	24
1.09	25
1.07	26
1.05	27
1.03	28
1.00	29

7 Runs	
ρ	df_{WL}
3.27	7
2.42	8
2.06	9
1.85	10
1.71	11
1.61	12
1.54	13
1.48	14
1.42	15
1.38	16
1.35	17
1.31	18
1.29	19
1.26	20
1.24	21
1.22	22
1.20	23
1.18	24
1.16	25
1.14	26
1.13	27
1.11	28
1.10	29
1.08	30
1.07	31
1.05	32
1.03	33
1.00	34

Abbreviations: σ_R, manufacturer's claim for repeatability; σ_{WL}, manufacturer's claim for within-laboratory imprecision; df_{WL}, degrees of freedom for within-laboratory imprecision.

Upper Verification Limit

Using the degrees of freedom, $df = df_R$ or $df = df_{WL}$, as appropriate, determine the UVL factor *F* from Table 7 at the entry corresponding to the intersection of the *df* with the total number of test samples used in the entire precision verification study.

Finally, calculate the UVL as the UVL factor *F* times the relevant claim, with the claim expressed, as needed for the comparison, either as an SD ($\sigma = \sigma_R$ or $\sigma = \sigma_{WL}$) or as a %CV (%CV = %CVR or %CV = $\%CV_{WL}$):

$$\text{UVL} = F \bullet \sigma \text{ or } \text{UVL} = F \bullet \%\text{CV} \quad (7)$$

Table 7. UVL Factors (*F*) as a Function of *DF* and Number of Samples (One to Six) in the Experiment

Number of Samples						
DF	**1**	**2**	**3**	**4**	**5**	**6**
5	1.49	1.60	1.66	1.71	1.74	1.76
6	1.45	1.55	1.61	1.65	1.67	1.70
7	1.42	1.51	1.56	1.60	1.62	1.65
8	1.39	1.48	1.53	1.56	1.58	1.60
9	1.37	1.45	1.50	1.53	1.55	1.57
10	1.35	1.43	1.47	1.50	1.52	1.54
11	1.34	1.41	1.45	1.48	1.50	1.52
12	1.32	1.39	1.43	1.46	1.48	1.49
13	1.31	1.38	1.42	1.44	1.46	1.47
14	1.30	1.37	1.40	1.42	1.44	1.46
15	1.29	1.35	1.39	1.41	1.43	1.44
16	1.28	1.34	1.38	1.40	1.41	1.43
17	1.27	1.33	1.36	1.39	1.40	1.41
18	1.27	1.32	1.35	1.37	1.39	1.40
19	1.26	1.31	1.34	1.36	1.38	1.39
20	1.25	1.31	1.34	1.36	1.37	1.38
21	1.25	1.30	1.33	1.35	1.36	1.37
22	1.24	1.29	1.32	1.34	1.35	1.36
23	1.24	1.29	1.31	1.33	1.35	1.36
24	1.23	1.28	1.31	1.32	1.34	1.35
25	1.23	1.28	1.30	1.32	1.33	1.34
26	1.22	1.27	1.30	1.31	1.32	1.34
27	1.22	1.26	1.29	1.31	1.32	1.33
28	1.22	1.26	1.28	1.30	1.31	1.32
29	1.21	1.26	1.28	1.30	1.31	1.32
30	1.21	1.25	1.27	1.29	1.30	1.31
31	1.20	1.25	1.27	1.29	1.30	1.31
32	1.20	1.24	1.27	1.28	1.29	1.30
33	1.20	1.24	1.26	1.28	1.29	1.30
34	1.20	1.24	1.26	1.27	1.28	1.29

Abbreviations: *DF*, degrees of freedom; UVL, upper verification limit.

NOTE:

Because of the limited sample size, **these statistical procedures are subject to false passes, and false failures.**

2.3.7 Interpreting Precision Verification Results

After all data analyses and consistency checks are complete, the user will have:

- Repeatability and within-laboratory imprecision estimates for each test sample in the study
- Results of the consistency checks (pass or fail) for each of these imprecision estimates

The final task is to assess the results of all consistency checks across all samples in the precision verification study. If all results are within the verification limits, the user precision is consistent with the manufacturer's claims. (**NOTE:** Because of the limited sample size, these statistical procedures are subject to false passes, and false failures.)

There are three principal scenarios:

- **Scenario 1A:** ***All estimates passed*** and were near or below the corresponding claims or UVLs. The overall study is consistent with the claims, and the data demonstrate that imprecision in the user's laboratory is comparable to what the manufacturer claims.

  Scenario 1B: ***All estimates passed, but some passed just barely*** and the distribution of results **suggests** that the imprecision exhibited in the user's laboratory could exceed the manufacturer claims, either overall or in a region of the stated measuring interval. Nevertheless, the study as a whole is statistically **consistent** with the claims. Due to the presence of results close to the UVL, however, daily QC results should be monitored carefully to ensure that the procedure's imprecision remains consistent with the claims.

- **Scenario 2:** ***Most estimates passed, but there were failures.*** The laboratory director should review the study as a whole in order to determine whether or not the procedure's imprecision, while apparently not fully consistent with the manufacturer claims, is still acceptable for use. If so, when signing off on the study, the director should include a rationale for the acceptability of the procedure's precision performance, and the imprecision exhibited by daily QC results should be carefully monitored.

- **Scenario 3:** ***Several estimates failed.*** The study as a whole is not consistent with the claims. The laboratory has several options. Besides rejecting the procedure outright, it may opt to troubleshoot the assay, perhaps with assistance from the manufacturer, and then repeat the entire precision verification study. Alternatively, the laboratory may opt to perform a larger study, using an experimental design consistent with recommendations in CLSI document EP05,[1] in order to characterize the procedure's imprecision performance with greater rigor.

2.3.8 Postverification Considerations

After the precision verification study is successfully completed and the procedure is put into routine operation, internal QC results often serve as the principal source of feedback of ongoing procedure precision (unless patient samples are regularly processed in duplicate or frequently repeated as described in CLSI document C24[21]).

Assigned QC limits should be in agreement with the manufacturer claims and the verification study's estimates for within-laboratory imprecision. The precision verification study yields estimates of within-laboratory imprecision over the course of approximately just one week, whereas monitoring results from testing control materials over longer periods yields estimates for a time frame more similar to that within which the manufacturer's claims were likely established. Indeed, statistics accumulated daily from testing control materials over time represent independent estimates of within-laboratory imprecision if the controls are processed in singlicate.

Over time, however, it is possible that imprecision estimates based on daily QC results may exceed the manufacturer's claims. This may reflect the presence of additional sources of variation that were not accounted for in the original precision study, such as reagent or calibrator lot changes, major maintenance events, changes in reagent stability, changes to laboratory environmental factors, effect of new operators or preexamination (preanalytical) factors, and so on.

IMPORTANT NOTE:

Statistics accumulated daily from testing control materials over time represent **independent estimates of within-laboratory imprecision** if the controls are processed in singlicate.

2.3.9 Some Possible Causes of Poor Performance or Failures

The UVL factors in Table 7 were constructed to maintain a 95% confidence level, hence a 5% false rejection rate, independent of the number of samples used in the study. Thus, for a given set of samples and precision type, the probability of a failure due to chance should be one in 20. For a given set of samples, the probability of failing due to chance for **either** repeatability **or** within-laboratory imprecision could therefore approach 10%, but this depends on the degree to which the two imprecision estimates are correlated, as well as other considerations.

Poor results in the precision verification study may reflect inadequate technique in performing the procedure or in managing systems components associated with the procedure.

IMPORTANT NOTE:

Poor results in the precision verification study **may reflect inadequate technique in performing the procedure or in managing systems components** associated with the procedure.

Poor results may be caused by:

- Improper storage of reagents
- Improper handling of the reagents
- Improper sample handling or stability issues
- Matrix differences between the user's samples and those used by the manufacturer to develop the precision claim, eg, plasma vs nonplasma liquid control materials
- Poor pipetting technique, if the procedure requires manual pipetting
- Substandard maintenance of the instrumentation used for the procedure
- Testing environment in the user laboratory, such as temperature, humidity, electrical, or radio frequency interference

Any of these causes may increase the apparent variability of the procedure in ways that do not reflect on the inherent variability of the procedure itself. Advice from the manufacturer may help determine the source of poor precision results.

If within-laboratory precision claims are verified while repeatability claims are not, this outcome may reflect benign differences in the operational definition of a "run." In particular, the manufacturer's repeatability estimates may often arise from testing a pair of adjacent replicates, whereas the user's experimental design could involve a greater time frame.

This guideline assumes that the manufacturer's precision claims accurately represent the procedure's current performance; it also assumes that the claims are known without appreciable uncertainty. There is uncertainty associated with the imprecision statistics tabulated in the PI. There is additional uncertainty associated with extracting from the PI table claims for measurand concentrations of the samples in the precision verification study, because the guideline assumes that straightforward interpolation can provide accurate estimates of imprecision at measurand levels other than those reported in the PI. Hence, one or both of the claims used in analyzing that study, namely σ_R and σ_{WL}; and their ratio, ρ, may be somewhat in error.

The precision study tabulated in the procedure's PI may have been determined from a less rigorous experiment involving fewer days than the classical CLSI document EP05[1] design. Within-laboratory imprecision estimates obtained in this manner are less robust than those developed over the minimum time period specified for the classic experiment within CLSI document EP05,[1] which calls for assaying each of several samples on at least 20 days, with two runs per day, and two replicates per run.

If for a given measurand concentration and precision type, the manufacturer's claim is much better than the clinically allowable limit of variability, it can happen that the user precision estimate likewise falls within this limit while

exceeding the UVL calculated from the claim. In this situation, the laboratory director may choose to accept the procedure's precision performance, even though the precision verification study failed to verify the claim. This can lead to the occurrence of Scenario 2, as described in Section 2.3.7.

Essentially, the same situation may arise if the PI includes both "worst-case" and typical ("representative") claims. For a given sample, one or both of the user precision estimates may exceed the UVL calculated from the PI typical performance table, but still fall within the limits claimed for worst-case performance. It would be wise to consult with the manufacturer because the precision verification study suggests that the results observed by the user are incompatible with what the manufacturer presents as representative precision performance for the procedure.

2.3.10 Worked Example: Serum Ferritin Procedure

To illustrate the entire process, from planning to final resolution, this section works through a complete precision verification study. As noted below, in order to provide a complete set of numerical examples suitable for checking software results, **more computations are provided than necessary** in this example to evaluate the data and determine the status of the individual precision estimates.

Context, Study Design, Implementation. The study was performed by a laboratory in the process of switching from a manual procedure for ferritin to a fully automated procedure with a measuring interval of 10 to 1000 µg/L. The laboratory adopted the recommended 5 × 5 study design—five days, five replicates per run—with all samples processed in a single run each day.

Due to the apparent dependency of precision on measurand concentration and because both low and high deviations from "normal" are of clinical interest for circulating ferritin, the laboratory opted to use three test samples. Rather than rely on the manufacturer's buffer-based controls, the laboratory prepared samples by pooling and aliquotting remnant patient sera, providing enough materials to allow two additional runs (if needed) beyond the five runs planned. Pooling based on results previously obtained with the manual procedure yielded samples with mid-range and abnormally elevated levels and a third level close to the lower reference limits, addressing the new procedure's measuring interval while remaining within the interval spanned by the PI table.

Runs were scheduled for alternating morning and afternoon sessions, in order to obtain data representative across shifts and operators, with manufacturer's controls included in each run. Because the precision claims in the PI were described as reflecting multiple calibration events, the laboratory decided (after consultation with the manufacturer) to calibrate the procedure before each run, even though the PI requires calibration only once per month. Individual sample and QC results were reviewed on a daily basis immediately after the completion of each run, and again (by a different reviewer) at the end of the study, before the data analysis. No errors were noted, and there were no missing results.

IMPORTANT NOTE:

In order to provide a complete set of numerical examples suitable for checking software results, **more computations are provided than necessary in this example to evaluate the data and determine the status of the individual precision estimates.**

Raw Data. Table 8 lists the 25 results for each sample vertically in the order in which they were generated, identified by run and replicate number. Figure 3 displays simple plots of these datasets, adequate for surveying both the consistency of distributions from run to run and the consistency of individual results relative to the bulk of the data for each sample. Only one point stands out as potentially aberrant, ie, the third result obtained for Sample 1 (Run 1, Replicate 3, 30.2 µg/L). Figure 3 is an example of plotting the results of the experiment; the user may choose another type of plot, such as connecting the results in the sequence in which they were obtained.

Table 8. Raw Data for Tri-Level Ferritin Example: Results in Order of Generation (units: µg/L)

Run	Replicate	Sample 1	Sample 2	Sample 3
1	1	26.6	140	606
1	2	25.2	139	627
1	3	30.2	138	621
1	4	27.6	138	606
1	5	25.6	140	620
2	1	24.3	140	612
2	2	25.7	143	610
2	3	23.8	141	611
2	4	25.3	143	595
2	5	24.1	137	630
3	1	26.1	140	649
3	2	24.0	138	626
3	3	25.4	136	636
3	4	26.0	141	639
3	5	24.3	136	648
4	1	26.5	141	615
4	2	27.1	144	633
4	3	25.9	142	605
4	4	25.5	143	616
4	5	25.5	144	625
5	1	24.5	139	622
5	2	26.4	140	632
5	3	25.8	141	646
5	4	26.0	138	619
5	5	25.1	141	623

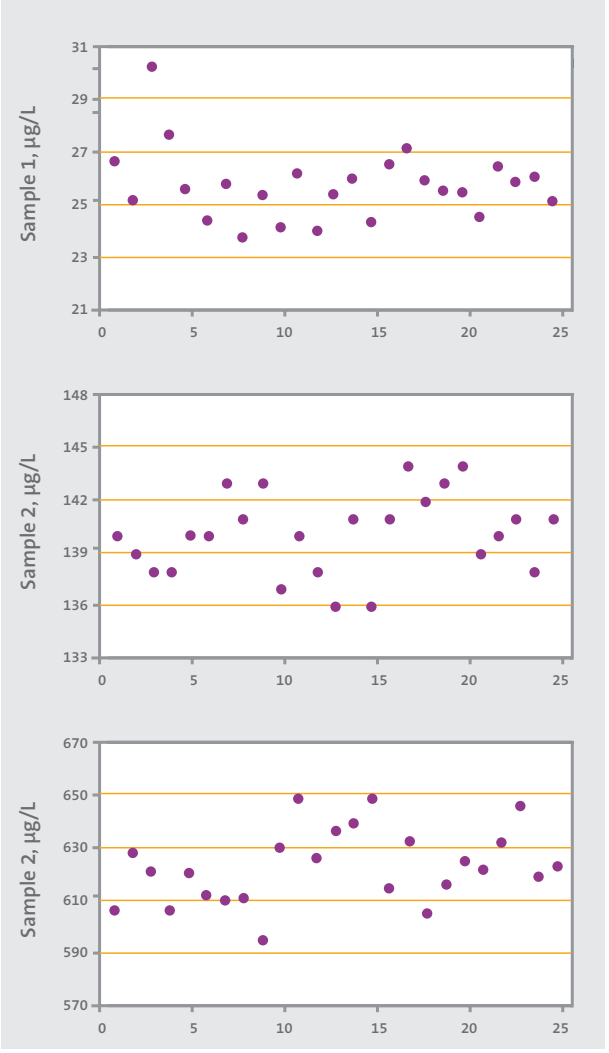


Figure 3. Results Plotted in Order of Generation (units = µg/L)

Table 9 summarizes the basic statistics needed in subsequent data analyses for all samples, along with calculations relevant to identifying individual results as statistical outliers by the Grubbs' test. Although only Sample 1 required the Grubbs' test, the test was performed on all three samples simply to provide additional illustrations of the calculations. The "Sample 1*" column provides statistics for Sample 1 after eliminating the suspect point. This sample is an **unbalanced** dataset because not all runs have the same number of results; the other samples are all balanced (five runs of five replicates each).

Table 9. Ferritin Example: Basic Statistics and "Outlier" Limits (units: µg/L)

	Sample 1	Sample 1*	Sample 2	Sample 3
N	25	24	25	25
$\bar{\bar{x}}$ (grand mean, µg/L)	25.7	25.5	140.1	622.9
SD, µg/L (%CV)	1.35 (5.2%)	0.99 (3.9%)	2.30 (1.6%)	14.1 (2.3%)
Lowest result, µg/L	23.8	23.8	136	595
Highest result, µg/L	30.2	27.6	144	649
Grubbs' lower limit, µg/L	21.48	N/A	132.9	578.7
Grubbs' upper limit, µg/L	29.92	N/A	147.3	667.1

* One result eliminated: Run 1, Replicate 3, 30.2 µg/L—a statistical outlier by the Grubbs' test (α = 0.01).
Abbreviations: %CV, coefficient of variation expressed as a percentage; N/A, not applicable; SD, standard deviation.

The mean, SD, and %CV were calculated from all individual results for each sample (N = 24 or 25, depending on the sample). The outlier limits are calculated from the mean and SD using the Grubbs' factor $G = 3.135$ (read from Table 3 for N = 25). As shown in Table 9, the highest result obtained for Sample 1 (30.2 µg/L) qualifies as a statistical outlier because it exceeds the upper Grubbs' limit (29.92 µg/L). A value so many SDs from the mean should occur less than 1% of the time due to chance alone; it is a very unusual point. Deleting it here is consistent with the conditions given in Section 2.3.4. Note that eliminating this point reduces the mean only slightly but has a considerable effect on the SD and %CV.

ANOVA. Table 10 summarizes the computations leading to the imprecision estimates for all samples. The between-run and within-run "mean squares" (*MS1* and *MS2*, respectively) came from the summaries generated by commercial one-way ANOVA software. The "average" number of results per run, n_0, came from Table 3; $\bar{\bar{x}}$ is the grand mean previously computed in Table 9. The between-run and within-run variance components (V_B, V_W) and the repeatability and within-laboratory imprecision estimates (S_R, S_{WL}, and the corresponding %CVs) were computed from the ANOVA table values.

Table 10. Ferritin Example: ANOVA Results and Imprecision Estimates

µg/L	Sample 1	Sample 1*	Sample 2	Sample 3
N	25	24	25	25
MS1 (between)	4.238	2.0851	15.86	626.56
MS2 (within)	1.3284	0.74137	3.16	113.52
n_0	5	4.79	5	5
V_B (between)	0.58192	0.28052	2.54	102.61
V_W (within)	1.3284	0.74137	3.16	113.52
$\bar{\bar{x}}$	25.7	25.5	140.1	623
S_R, µg/L (%CV)	1.15 (4.5%)	0.86 (3.4%)	1.78 (1.3%)	10.7 (1.7%)
S_{WL}, µg/L (%CV)	1.38 (5.4%)	1.01 (4.0%)	2.4 (1.7%)	14.7 (2.4%)

* One result was eliminated as a statistical outlier.
Abbreviations: %CV, coefficient of variation expressed as a percentage; ANOVA, analysis of variance; *MS*, mean squares; S_R, user estimate for repeatability; S_{WL}, user estimate for within-laboratory imprecision; V_B, variance between runs; V_W, variance within run.

PI Claims. Table 11 summarizes the manufacturer's imprecision table from the ferritin procedure's PI.

Table 11. Ferritin Example: Imprecision Claims From the Manufacturer's PI

	Mean, µg/L	Repeatability SD, µg/L (%CV)	Within-Laboratory Imprecision, µg/L (%CV)
PI Claim 1	13.2	0.43 (3.3%)	0.70 (5.3%)
PI Claim 2	102	2.0 (2.0%)	3.5 (3.4%)
PI Claim 3	211	2.9 (1.4%)	5.1 (2.4%)
PI Claim 4	429	6.9 (1.6%)	12.0 (2.8%)
PI Claim 5	878	15.8 (1.8%)	23.7 (2.7%)

Abbreviations: %CV, coefficient of variation expressed as a percentage; PI, package insert; SD, standard deviation.

UVLs. For most of the user estimates in this example, consistency with the manufacturer claims—their "pass/fail" status—can be determined by visual inspection without having to calculate more than a few UVLs. Nevertheless, UVLs are provided for all of the PI claims to illustrate the calculations involved.

The UVL calculations are summarized for this example in Table 12. For repeatability, the degrees of freedom, df_R, are based on the design of the user's experiment—specifically, on the actual number of runs, $k = 5$, and the intended number of **replicates** per run, $n = 5$. For within-laboratory imprecision, however, the degrees of freedom, df_{WL}, depend not only on the experimental design but also on the claims ratio $\rho = \sigma_{WL} / \sigma_R$. After determining ρ, df_{WL} was obtained from Table 6. For both precision types, the UVL, whether expressed as an SD or as a %CV, was calculated by multiplying the corresponding claim by the UVL factor *F* obtained from Table 7 (using the column for three samples in the user's precision verification study).

Table 12. Ferritin Example: UVLs Calculated for PI Precision Claims

	PI Claim 1	PI Claim 2	PI Claim 3	PI Claim 4	PI Claim 5
Mean, µg/L	13.2	102	211	429	878
Repeatability Imprecision					
σ_R, µg/L (%CV)	0.43 (3.3%)	2.0 (2.0%)	2.9 (1.4%)	6.9 (1.6%)	15.8 (1.8%)
k	5	5	5	5	5
n	5	5	5	5	5
df_R	20	20	20	20	20
F	1.34	1.34	1.34	1.34	1.34
UVL_R, µg/L (%CV)	0.58 (4.4%)	2.7 (2.6%)	3.9 (1.8%)	9.2 (2.2%)	21.2 (2.4%)
Within-Laboratory Imprecision					
σ_{WL}, µg/L (%CV)	0.70 (5.3%)	3.5 (3.4%)	5.1 (2.4%)	12.0 (2.8%)	23.7 (2.7%)
ρ	1.63	1.75	1.76	1.74	1.50
df_{WL}	8	7	7	7	9
F	1.53	1.56	1.56	1.56	1.50
UVL_{WL}, µg/L (%CV)	1.07 (8.1%)	5.5 (5.4%)	8.0 (3.8%)	18.7 (4.4%)	35.6 (4.0%)

Abbreviations: %CV, coefficient of variation expressed as a percentage; σ_R, manufacturer's claim for repeatability; σ_{WL}, manufacturer's claim for within-laboratory imprecision; df_R, degrees of freedom for repeatability; df_{WL}, degrees of freedom for within-laboratory imprecision; PI, package insert; UVL, upper verification limit; UVL_R, upper verification limit (repeatability); UVL_{WL}, upper verification limit (within-laboratory).

Useful Rule of Thumb. UVLs are generally (at least) about 30% higher than their corresponding imprecision claims. The usefulness of this rule of thumb in minimizing the need for exacting calculations is noted below.

Status of the Individual Sample Estimates. The first five columns of Tables 13 and 14 (the tables are sorted by mean measurand concentration [second column]) provide an easily constructed overview of how the several user estimates for repeatability and within-laboratory imprecision relate to the PI claims and their associated UVLs. (CLSI's StatisPro[2] also generates graphs to aid in visualizing these relationships. See Section B1 in Appendix B for examples based on the same ferritin dataset.)

The goal at this stage is to determine the pass/fail status (sixth column) of the user sample estimates by inspection. For this example, estimates, claims, and UVLs are all tabulated as %CVs; alternatively, they could be tabulated as SDs, if that would better facilitate the comparisons. Mean values, estimates, and claims (second, third, and fourth columns) come from Tables 10 and 11; while the UVLs (fifth column) come from Table 12. In this example, as noted below, the calculated UVLs are actually not required (hence, neither is Table 12) because the pass/fail determinations can all be made by reference to the claims, supplemented by invoking the Useful Rule of Thumb, as needed, to roughly approximate the UVLs.

IMPORTANT NOTE:

UVLs are generally (at least) about 30% higher than their corresponding imprecision claims. The usefulness of this rule of thumb in minimizing the need for exacting calculations is noted below.

REMINDER:

StatisPro[2] also generates graphs to aid in visualizing these relationships.

Table 13. Ferritin Example: Repeatability: User Sample Estimates, Expressed as %CVs, Merged With PI Claims and UVLs

µg/L	Mean	Estimate	Claim	UVL	Status
PI Claim 1	13.2		3.3%	4.4%	
Sample 1*	25.5	3.4%			Pass
Sample 1	25.7	4.5%			– Fail –
PI Claim 2	102		2.0%	2.6%	
Sample 2	140	1.3%			Pass
PI Claim 3	211		1.4%	1.8%	
PI Claim 4	429		1.6%	2.2%	
Sample 3	623	1.7%			Pass
PI Claim 5	878		1.8%	2.4%	

* One result was eliminated as a statistical outlier.
Abbreviations: %CV, coefficient of variation expressed as a percentage; PI, package insert; UVL, upper verification limit.

Sample 1. With an observed mean ($\bar{\bar{x}}$) of just over 25 µg/L, this sample might be regarded as sufficiently close to the 13.2 µg/L mean for PI Claim 1 to warrant comparison to just that claim, on a "nearest neighbor" basis. If so, the 3.4% repeatability estimate obtained after eliminating the statistical outlier rates a pass because, even though slightly higher than the 3.3% claim (invoking the Rule of Thumb here) it is well within 30% of that claim. Arguably, however, the sample is better regarded as falling in between the means for PI Claims 1 and 2 (and closer to the first claim than the second), making interpolation the more appropriate evaluation method. If so, the 3.4% repeatability estimate obtained for Sample 1 after eliminating the outlier again rates a pass, though perhaps just barely, on interpolating between the UVLs calculated—or simply roughly approximated by the Useful Rule of Thumb—for PI Claims 1 and 2. (The 4.5% estimate obtained **without** eliminating the outlier fails, because it exceeds both of the neighboring UVLs.)

Sample 2. The 1.3% repeatability estimate clearly passes because it is less than any of the claims for this precision type.

Sample 3. The 1.7% repeatability estimate (**NOTE:** no calculation performed) falls in between the claims (1.6% and 1.8%) at bracketing concentration levels, and it passes easily with respect to the calculated or estimated UVLs for PI Claims 4 and 5.

Table 14. Ferritin Example: Within-Laboratory Imprecision: User Sample Estimates, Expressed as %CVs, Merged With PI Claims and UVLs

µg/L	Mean	Estimate	Claim	UVL	Status
PI Claim 1	13.2		5.3%	8.1%	
Sample 1*	25.5	4.0%			Pass
Sample 1	25.7	5.4%			Pass
PI Claim 2	102		3.4%	5.4%	
Sample 2	140	1.7%			Pass
PI Claim 3	211		2.4%	3.8%	
PI Claim 4	429		2.8%	4.4%	
Sample 3	623	2.4%			Pass
PI Claim 5	878		2.7%	4.0%	

* One result was eliminated as a statistical outlier.
Abbreviations: %CV, coefficient of variation expressed as a percentage; PI, package insert; UVL, upper verification limit.

Sample 1. The 4.0% within-laboratory imprecision estimate obtained after eliminating the statistical outlier falls well below PI Claim 1, namely 5.3%, and also below the average of the two claims, (5.3 + 3.4) / 2 = 4.35%, on either side of the sample. So, the estimate passes, no matter whether a nearest neighbor rule or an interpolation rule is regarded as more appropriate. (Indeed, even the 5.4% estimate obtained **without** eliminating the outlier passes, because it does not exceed the calculated UVLs for PI Claims 1 and 2.)

Sample 2. The 1.7% within-laboratory imprecision estimate passes, being less than any of the claims for this precision type.

Sample 3. The 2.4% within-laboratory imprecision estimate passes, being less than the two neighboring claims (2.8% and 2.7%).

Conclusion. With the aberrant result for Sample 1 justifiably treated as a statistical outlier, the user estimates for repeatability and within-laboratory imprecision pass for all three of the samples. Because all six estimates pass **individually,** the precision verification study **as a whole** also passes; that is, **in aggregate,** the estimates are consistent with the manufacturer's PI claims. Looking more closely at the data, one can see that performance in the study at mid-range and elevated ferritin levels appears entirely unproblematic (good confirmation of the claims), whereas careful monitoring of precision at very low levels may be advisable.

This page is intentionally left blank.

Chapter 3

Estimation of Bias by Testing Materials With Known Concentrations

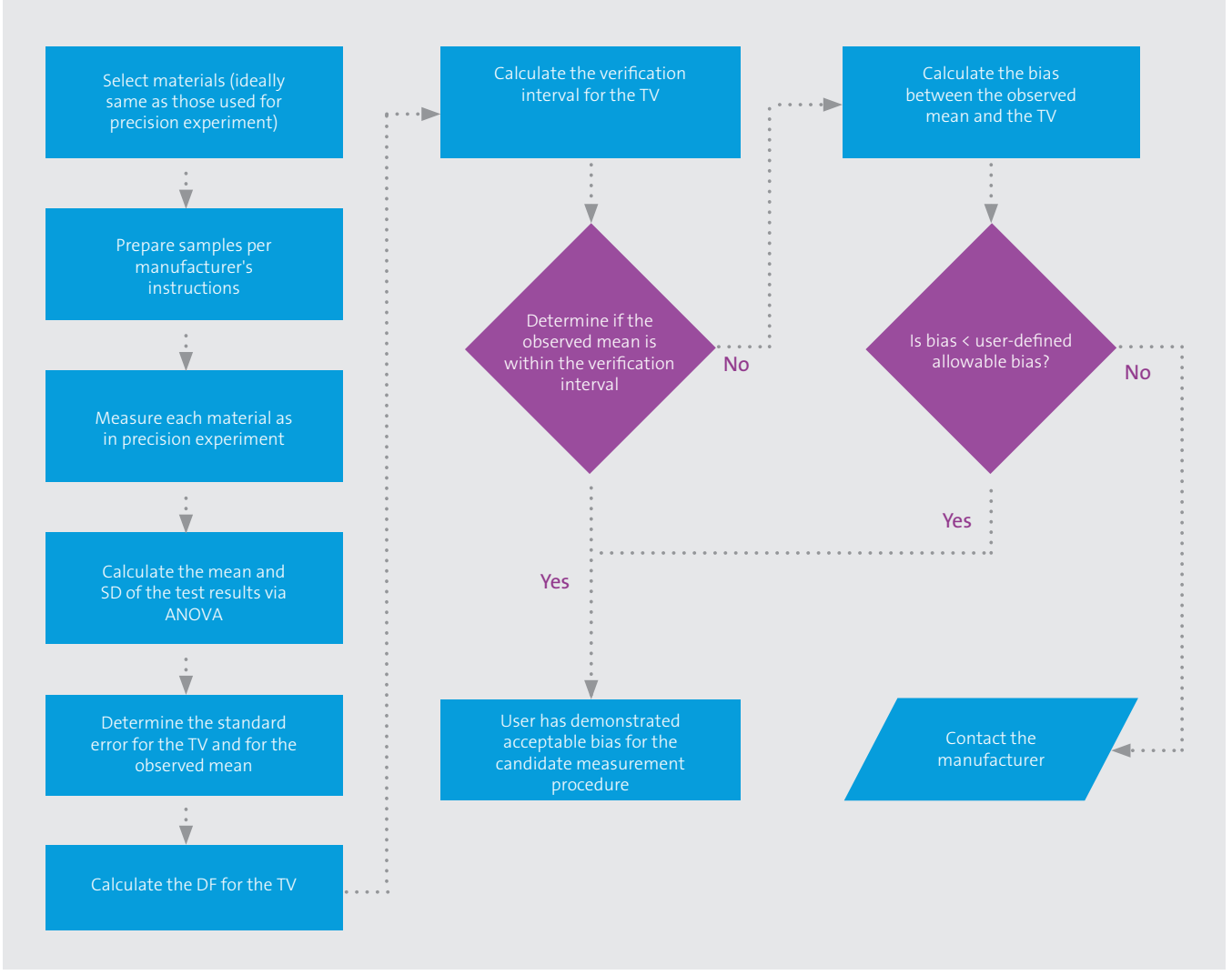
This chapter includes:

- Overview of the estimation of bias using materials with known concentrations
- Guidance on selecting reference materials, target value, mean value, and standard errors
- Verification interval calculations
- Worked examples

3 Estimation of Bias by Testing Materials With Known Concentrations

3.1 Overview of the Bias Experiment

Bias is assessed by analyzing materials with known concentration—such as PT materials and/or other reference standards—and comparing the results for the measurement procedure under evaluation to the TVs. When materials of this kind are also suitable for verifying precision, a single experiment can yield estimates of both imprecision and bias. Figure 4 depicts a flow chart for the experiment.



Abbreviations: ANOVA, analysis of variance; *DF*, degrees of freedom; SD, standard deviation; TV, target value.

Figure 4. Overview of the Estimation of Bias Using Materials With Known Concentrations (see Section 3.1)

Before initiating the experiment, the user should specify the allowable bias, as described in Chapter 1. Even if the bias observed in this experiment is statistically significant, it may still be clinically acceptable. This can be determined by comparison with the allowable bias limits.

This section describes a process, involving repeated measurements of materials ("reference materials") with known concentrations, herein called its TV, for verifying that the bias of a measurement procedure is within allowable limits at one or more clinically relevant measurand concentrations. This type of experiment for "demonstrating trueness" is also called a "recovery" or "bias estimation" study. For the bias estimation study, two statistics must be derived from the data:

- The overall mean, $\bar{\bar{x}}$, of the experiment (eg, "5 × 5" measurements)
- The overall mean's standard error ($se_{\bar{\bar{x}}}$).

Section 3.4 describes the calculations involved.

In brief, having the TV and the calculated $\bar{\bar{x}}$, the first step is to calculate the difference (bias) between the two. The next step is to calculate the standard error of this difference (se_c). The final calculation is defining a verification interval (*VI*) that has a 95% probability of containing the true difference. This calculation is achieved by multiplying the standard error by a "coverage factor," k, $VI = k \bullet se_c$. The multiplier, k, typically has a value on the order of 2 or 3 to reach a probability of 95% and 99%, respectively. The calculated bias is then assessed in light of the verification interval and allowable error limit. Section 3.5 describes the calculations involved, and it includes tables simplifying the computations for experiments consisting of five to seven runs, with five replicates per run. Section 3.6 discusses the interpretation of results, and Section 3.7 presents several worked examples.

Depending on what materials with known concentration are adopted, the study can serve one or more of several purposes, including to:

- Demonstrate agreement with the stated value of a recognized standard material by estimating the bias of a measurement procedure.
- Verify the trueness of a measurement procedure relative to its peer group by estimating bias using PT or peer group QC materials.
- Verify the recovery of an assigned concentration of a material especially prepared for this purpose by a manufacturer.
- Estimate the measurement procedure's bias when there are not enough patient samples to perform an adequate measurement procedure comparison (see CLSI document EP09[6]), or when no suitable reference measurement procedure is available.
- Obtain additional verification of trueness at specific concentrations after performing a patient sample-based method comparison.

REMINDER:

Before initiating the experiment, the user should specify the allowable bias, as described in Chapter 1. Even if the bias observed in this experiment is statistically significant, it may still be clinically acceptable. **This can be determined by comparison with the allowable bias limits.**

Besides having a suitable composition (matrix), each reference material must have a known concentration assigned by a reference measurement procedure, for example, or based on peer group data from PT or interlaboratory QC programs. (There are several options.) It is also essential to have an estimate of the TV's **uncertainty,** expressible as a standard error (se_{RM}). Sections 3.2 and 3.3 provide guidance on selecting the best available reference materials and determining their standard errors, respectively.

The experimental design described here is essentially the same as the design described in Chapter 2 for verifying precision claims, and some elements of the data analysis are also the same, making it desirable to implement both studies as a single experiment. The "5 × 5" experimental design described for the precision verification study in Chapter 2 is likewise recommended for processing the reference materials with the procedure in question as a basis for estimating its biases relative to the TVs of the reference materials. This process entails assaying each of the reference materials over five or more (not necessarily consecutive) days, with one run per day and five replicates per run, yielding a total of 25 results per sample, assuming there are no missing values and no results treated as statistical outliers.

Accordingly, processing the samples for both studies (precision verification and bias estimation) in tandem, that is, in the same runs, makes for efficient bench work and data analysis, because the calculations described in Chapter 2 can yield estimates needed in the bias assessment calculations.

NOTE:

Processing the samples for both studies (precision verification and bias estimation) in tandem, that is, in the same runs, makes for efficient bench work and data analysis, because the calculations described in Chapter 2 **can yield estimates needed in the bias assessment calculations.**

3.2 Selecting Reference Materials

Ordinarily, for the precision verification study discussed in Chapter 2, patient samples or pools thereof are clearly the "best available materials" for analysis. For the study discussed in this section, however, the choice is far from clear, because there are several competing considerations. It is up to the user laboratory to justify its choice of materials in light of considerations such as those below.

The laboratory's reasons for performing the recovery study are relevant to the choice of materials:

- Is the study being undertaken with the goal of verifying that bias exhibited by the measurement procedure in the user laboratory is consistent with expectations **for the measurement procedure,** ie, expectations set by peer group results from interlaboratory QC or PT? In this case, samples from a peer group QC program or a PT/EQA program and/or commercial controls with appropriate procedure-specific value assignments may represent the best choice.
- Is the goal to assess the procedure's bias relative to a particular reference standard? This goal will usually dictate the choice of material(s).

- Does the study's interest lie in assessing bias relative to some other commercial or laboratory-developed assay for the measurand in question, or perhaps to the **same** assay in use in another laboratory or at another site? In this case, the goal may be better served by performing a split-sample measurement procedure comparison study.

When the purpose of the evaluation is to introduce a new assay in the laboratory, the materials should represent at least two clinically relevant concentration levels, although the design of the experiment is suitable for use with only one material. The materials should either represent or be as fully commutable as possible with the patient sample types intended for analysis by the procedure; and they must be stable enough for the multiday experiment described in this section.

The materials must have TVs. This requirement generally rules out the use of freshly prepared patient sample pools.

Moreover, the quality of the TV assignments is important. How rigorously have they been determined? And, are the **uncertainties** associated with the TVs (uncertainties expressed quantitatively as "standard errors" [see Section 3.3]) either declared or estimable from the experimental data or statistics associated with the value assignments? If not, the assigned values must be treated as if they were known without uncertainty, analogous to the way estimates of imprecision tabulated in the manufacturer's PI are treated in the precision verification study.

Finally, practical issues cannot be ignored. For example, are the materials available in sufficient quantity, and at a reasonable cost?

Some sources of testing materials with known concentrations are listed below, along with a few notes on their suitability or shortcomings.

- Materials for which concentrations can be adjusted to stated levels with negligible imprecision, eg, by spiking a therapeutic drug into patient sample pools known to be analyte free, will have TVs associated practically speaking, with no uncertainty and thus with standard errors appropriately set to zero.
- Reference standards are high order standards that are recognized by a professional body such as the International Federation of Clinical Chemistry and Laboratory Medicine, the National Institute of Standards and Technology (NIST), the Institute for Reference Materials and Measurements, or the Joint Committee for Traceability in Laboratory Medicine (JCTLM). For some analytes, certified reference materials are available from NIST and other internationally recognized providers. A partial list of these materials is available from JCTLM (http://www.bipm.org/jctlm). Bear in mind the metrological traceability issues involved with different measurands (see Appendix C) and the state of the art for reference measurement procedures (http://www.bipm.org/jctlm). Some

NOTE:

More information on split-sample method comparison studies **can be found in CLSI document EP09.**[6]

NOTE:

See CLSI document EP14[26] for more information on commutability of samples.

reference materials may not be appropriate for routine user laboratories due to considerations of commutability, stability, availability, or cost. They also may not be optimal for verifying performance relative to expectations for the assay in question or relative to experience with the user's previous assay.

- Survey materials from PT/EQA programs may consist of unadulterated patient sample-based materials with TVs assigned by the program organizers, based either on reference measurement procedures or on spiking with International Standards. If so, the uncertainties (standard errors) associated with the TVs can usually be obtained from the organizers if they are based on reference measurements, or else treated as negligible. In any case, survey materials from PT programs typically have both average values and SDs that reflect testing by a large, identifiable number of laboratories with a given measurement procedure (often across several reagent lots) or with a relevant family of procedures deemed essentially equivalent. It is often reasonable to adopt these averages as TVs representing expectations for the procedure in question. Moreover, reasonable estimates for the standard errors of these TVs can be derived from the reported SDs and the relevant numbers of participating laboratories.
- Similarly, materials used in interlaboratory QC programs have peer group means that can be adopted as TVs, providing the number of participants in the peer group is adequate. (In general, 10 [but desirably 20 or more] is considered the minimum for a reliable TV.) SDs are also reported, but estimating standard errors for the peer group–based TVs is somewhat problematic because the participating laboratories may differ markedly from one another in the number of values contributed by each to the database.
- Materials intended for routine internal QC or calibration verification of the measurement procedure in question generally have preassigned procedure-specific TVs and either SDs or expected "ranges" (concentration intervals) as well. However, the uncertainties associated with these TVs are rarely declared or estimable from the information supplied or available from the assay manufacturer of the measurement procedure or the third-party control vendor. In particular, the standard errors cannot be identified with SDs supplied by the manufacturer or back-calculated from the "ranges." This means that the user must treat the targets as if they were known without uncertainty, ie, as if they had standard errors of zero, which is seldom realistic. Moreover, without credible estimates of their uncertainty, the quality of the TVs remains in doubt, because there is no objective basis for judging their reliability.

- Patient sample pools or QC materials that have been repeatedly measured over a substantial period of time in one or more laboratories using the procedure in question or using an assay deemed essentially equivalent may constitute suitable materials for the recovery study described, providing the assembled database has been suitably tracked and analyzed (using techniques described in Section 2.2 or Section 3.4) to yield both means and statistics from which standard errors can be estimated. Thus, a central reference laboratory could establish TVs and standard errors for subsequent use by satellite laboratories, or a laboratory with a substantial backlog of QC results for a given procedure could use the same samples and relevant statistics extracted from the database for checking the bias of a new procedure relative to the procedure currently in use.
- Patient samples whose target concentrations have been established by use of a traceable reference quality measurement procedure may serve as reference materials. For example, a laboratory could submit a group of patient samples to a participating laboratory in the Cholesterol Reference Method Laboratory Network for lipid analyses and certificates of traceability.

3.3 Target Values and Their Standard Errors

At least two statistics, TV and se_{RM}, must be determined for each reference material, independent of the recovery (bias estimation) study. Depending on circumstances, an additional statistic—reflecting N-size or *DF*—may also be required, as indicated below.

- **Scenario A.** For bona fide reference materials, there should be no difficulty identifying TV. To reflect the extensive testing associated with value assignments for materials of this kind, set the *DF* to df_{RM} = infinity. As for se_{RM}:
  - If the manufacturer supplies a "standard error" or "standard uncertainty" (abbreviated by lowercase "*u*") or "combined standard uncertainty" (often denoted by "u_c") for the TV, set se_{RM} equal to the stated standard error, standard uncertainty, or combined standard uncertainty.
  - If the manufacturer supplies an "expanded uncertainty" (abbreviated by uppercase "*U*") for the TV, then either the "coverage factor" (abbreviated by "*k*") or the "coverage" (eg, 95% or 99%) will be specified as well. If *k* is the coverage factor, set $se_{RM} = U / k$; if the coverage is 95%, set $se_{RM} = U / 1.96$; if the coverage is 99%, set $se_{RM} = U / 2.58$.
  - If the manufacturer reports the lower and upper limits of a 95% or 99% confidence interval (CI) for the TV, ie, 2 • *U* (*k* = 1.96 and *k* = 2.58, respectively), set se_{RM} = (*Upper* – *Lower*) / (2 • 1.96) for a 95% CI; and set se_{RM} = (*Upper* – *Lower*) / (2 • 2.58) for a 99% CI.

- **Scenario B.** If the reference material has a TV determined by PT consensus results, then both an SD (identified as SD_{RM}) based on these results and the number of laboratories reporting (identified as *nLab*) should also be available. In this scenario, set $se_{RM} = SD_{RM}/\sqrt{nLab}$ and $N_{RM} = nLab$.
- **Scenario C.** If the reference material has a TV determined by peer group results from an interlaboratory QC program, set se_{RM} and N_{RM} as described above for the PT scenario. In this case, the statistics must be considered somewhat problematic, as the dataset will likely reflect multiple results from most laboratories, and some laboratories may contribute far more results than others.
- **Scenario D.** If the TV represents a conventional quantity value, set $se_{RM} = 0$ and df_{RM} = infinity.
- **Scenario E.** When working with a commercial QC material supplied with a TV for which the standard error cannot be estimated, set $se_{RM} = 0$. In effect, this scenario defaults to assuming that the material's concentration is known without any uncertainty (see Scenario D). Accordingly, the verification interval will be narrower, and the probability of the user's average result, $\bar{\bar{x}}$, falling outside that interval will be higher than if the TV's uncertainty were known.

IMPORTANT NOTE:

This approach may be superior when **analysis of the precision verification study indicates that performance in the user's laboratory is consistent with the manufacturer's precision claims,** which can be assumed to reflect a larger, more definitive study. On the other hand, this advantage may be offset by uncertainties arising from the need to interpolate from the PI table.

3.4 Mean Values and Their Standard Errors

Set $\bar{\bar{x}}$ to the mean of all results obtained for the sample in the recovery study, and set the *DF* to $df_{\bar{\bar{x}}} = nRun - 1$.

$se_{\bar{\bar{x}}}$ can be calculated in several ways, which, for present purposes, should yield equally good (roughly equivalent) estimates:

- In the formula below, *nRun* is the **number of runs** in the experiment and *nRep* is the **number of replicates** per run. (In case of any missing values, set *nRep* to the **average** number of results per run to allow the use of balanced ANOVA calculations or perform ANOVA directly if the analysis software supports use of unbalanced data sets.) Using estimates obtained in the study for the sample's repeatability (s_r) and within-laboratory imprecision (s_{WL}), set:

$$se_{\bar{\bar{x}}} = \sqrt{\frac{1}{nRun}\left[s_{WL}^2 - \left(\frac{nRep-1}{nRep}\right)s_r^2\right]} \qquad (8)$$

- Perform calculations as above, but substitute for s_r and s_{WL} the measurement procedure manufacturer's repeatability (σ_r) and within-laboratory imprecision (σ_{WL}) claims derived from the precision table in the procedure's PI, as discussed in Section 2.3.6.1. This approach may be superior when analysis of the precision verification study indicates that performance in the user's laboratory is consistent with the manufacturer's precision claims, which can be assumed to reflect a larger, more definitive study.

On the other hand, this advantage may be offset by uncertainties arising from the need to interpolate from the PI table.

- If s_{WL} and the *DF* of $\bar{\bar{x}}$ are known, an equivalent equation for calculating $se_{\bar{\bar{x}}}$ is given by:

$$se_{\bar{\bar{x}}} = s_{WL} \; / \sqrt{df_{\bar{\bar{x}}} + 1} \qquad (9)$$

3.5 The Verification Interval

First, calculate the combined standard error (se_C) from $se_{\bar{\bar{x}}}$ and se_{RM}:

$$se_C = \sqrt{se_{\bar{\bar{x}}}^2 + se_{RM}^2} \qquad (10)$$

When $se_{RM} = 0$, this reduces to $se_C = se_{\bar{\bar{x}}}$.

Then, to determine the **combined** *DF* (df_C) from $df_{\bar{\bar{x}}}$ and df_{RM} in accordance with Satterthwaite's approximation, evaluate the following equation:

$$df_C = \frac{(se_{\bar{\bar{x}}}^2 + se_{RM}^2)}{\frac{se_{\bar{\bar{x}}}^4}{df_{\bar{\bar{x}}}} + \frac{se_{RM}^4}{df_{RM}}} \qquad (11)$$

It should rarely be necessary to evaluate the Satterthwaite formula directly, as the following shortcuts will be applicable in many situations:

- When $se_{RM} = 0$, as in Scenario E in Section 3.3, this formula reduces to $df_C = df_{\bar{\bar{x}}}$.
- When $se_{RM} > 0$ but df_{RM} = infinity, as in Scenarios A and D in Section 3.3, the formula reduces to:

$$df_C = df_{\bar{\bar{x}}} \cdot (se_C / se_{\bar{\bar{x}}})^4 \qquad (12)$$

- In Scenarios B (PT) and C (peer group QC) in Section 3.3, providing that the experimental design involved five, six, or seven runs with five replicates per run, Table 15A, 15B, or 15C, respectively, can obviate the need to evaluate the Satterthwaite formula. Enter the appropriate table with N_{RM} set to the number of laboratories and $tau = se_{RM} / se_{\bar{\bar{x}}}$, and read off df_C. The tables stop at 200 laboratories because the width of the verification interval changes only minimally after the number of laboratories exceeds 200. Interpolation of numbers of laboratories is not necessary; use the table entry that most closely matches the number of laboratories (see Worked Example 1A in Section 3.7.1).

NOTE:

The tables stop at 200 laboratories because the width of the verification interval changes only minimally after the number of laboratories exceeds 200. Interpolation of numbers of laboratories is not necessary; use the table entry that most closely matches the number of laboratories (see Worked Example 1A in Section 3.7.1).

Now set the multiplier *m* to the Student's *t* quantile for a probability of 0.975 (this corresponds to a confidence level of 95%) and df_C:

$$m = t(0.975, df_C) \quad (13)$$

NOTE: When a 95% confidence level is desired, the use of a probability of 0.975 is correct for recovery experiments involving just one sample, but experiments of this kind often involve multiple samples. (In particular, for demonstrations of trueness, as when introducing a new assay into the laboratory, this guideline recommends testing at least two samples representing different, medically relevant concentration levels.) To maintain a family-wise confidence level of 95% when the recovery experiment involves a number of samples given as *nSam*, assuming that all samples are of similar importance, use a probability of 1.0 – (0.025 / *nSam*); ie, use 0.975 for one sample, 0.9875 for two, 0.9917 for three, 0.9938 for four, 0.995 for five, and so on.

Finally, calculate the verification interval (*VI*) as:

$$VI = \mathrm{TV} \pm (m \bullet se_C) = \mathrm{TV} \pm (t_{0.975,df_C} \times se_C) \quad (14)$$

Table 15A. df_C for the Combined Standard Error of the Mean and TV as a Function of the Ratio of the Standard Error of the Reference Material to the Standard Error of the Mean ($tau = se_{RM}/se_{\bar{x}}$), for Five Runs, With Five Replicates per Run, and N_{RM} = 10, 20, 50, 100, and ≥ 200 Laboratories. **NOTE:** Table 15A is intended for use in Scenarios B (PT) and C (peer group QC) in Section 3.3, when the user's experiment involves five runs.

10 Laboratories		20 Laboratories		50 Laboratories		100 Laboratories		200 Laboratories	
tau	df_C	*tau*	df_C	*tau*	df_C	*tau*	df_C	*tau*	df_C
0.000	4	0.000	4	0.000	4	0.000	4	0.000	4
0.349	5	0.346	5	0.344	5	0.344	5	0.344	5
0.490	6	0.481	6	0.477	6	0.475	6	0.475	6
0.600	7	0.582	7	0.573	7	0.571	7	0.569	7
0.698	8	0.666	8	0.652	8	0.647	8	0.646	8
0.791	9	0.739	9	0.718	9	0.713	9	0.710	9
0.886	10	0.806	10	0.778	10	0.770	10	0.766	10
0.991	11	0.869	11	0.831	11	0.821	11	0.816	11
1.126	12	0.929	12	0.880	12	0.867	12	0.861	12
1.500	13	0.987	13	0.925	13	0.910	13	0.903	13
2.175	12	1.045	14	0.968	14	0.949	14	0.941	14
2.832	11	1.104	15	1.008	15	0.987	15	0.977	15
4.149	10	1.164	16	1.047	16	1.022	16	1.010	16
		1.227	17	1.084	17	1.055	17	1.042	17
		1.295	18	1.119	18	1.086	18	1.072	18
		1.369	19	1.154	19	1.117	19	1.101	19
		1.455	20	1.188	20	1.146	20	1.128	20
		1.561	21	1.221	21	1.174	21	1.154	21
		1.711	22	1.253	22	1.201	22	1.179	22
		2.179	23	1.285	23	1.227	23	1.203	23
		3.121	22	1.317	24	1.252	24	1.227	24
		4.070	21	1.348	25	1.277	25	1.249	25
		5.990	20	1.379	26	1.301	26	1.271	26
				1.410	27	1.325	27	1.292	27
				1.441	28	1.348	28	1.313	28
				1.472	29	1.370	29	1.333	29
				1.503	30	1.393	30	1.352	30
				1.850	40	1.598	40	1.527	40
				3.500	53	1.985	60	1.808	60
						4.975	103	2.528	120
								7.053	203
infinity	9	infinity	19	infinity	49	infinity	99	infinity	199

Abbreviations: df_C, combined degrees of freedom; PT, proficiency testing; QC, quality control; TV, target value.

Table 15B. df_C for the Combined Standard Error of the Mean and TV as a Function of the Ratio of the Standard Error of the Reference Material to the Standard Error of the Mean ($tau = se_{RM}/se_{\bar{x}}$), for Six Runs, With Five Replicates per Run, and NRM = 10, 20, 50, 100, and ≥ 200 Laboratories. NOTE: Table 15B is intended for use in Scenarios B (PT) and C (peer group QC) in Section 3.3, when the user's experiment involves six runs.

10 Laboratories		20 Laboratories		50 Laboratories		100 Laboratories		200 Laboratories	
tau	df_C	*tau*	df_C	*tau*	df_C	*tau*	df_C	*tau*	df_C
0.000	5	0.000	5	0.000	5	0.000	5	0.000	5
0.314	6	0.311	6	0.310	6	0.309	6	0.309	6
0.442	7	0.434	7	0.430	7	0.429	7	0.429	7
0.543	8	0.527	8	0.519	8	0.517	8	0.516	8
0.632	9	0.604	9	0.592	9	0.588	9	0.586	9
0.717	10	0.672	10	0.654	10	0.648	10	0.646	10
0.804	11	0.734	11	0.709	11	0.702	11	0.698	11
0.900	12	0.792	12	0.758	12	0.749	12	0.745	12
1.020	13	0.848	13	0.804	13	0.793	13	0.788	13
1.342	14	0.902	14	0.847	14	0.833	14	0.826	14
1.860	13	0.955	15	0.886	15	0.870	15	0.863	15
2.278	12	1.009	16	0.924	16	0.905	16	0.896	16
2.890	11	1.064	17	0.960	17	0.938	17	0.928	17
4.182	10	1.122	18	0.995	18	0.969	18	0.958	18
		1.183	19	1.028	19	0.999	19	0.986	19
		1.251	20	1.061	20	1.027	20	1.013	20
		1.328	21	1.092	21	1.055	21	1.039	21
		1.422	22	1.123	22	1.081	22	1.064	22
		1.553	23	1.153	23	1.107	23	1.087	23
		1.949	24	1.183	24	1.131	24	1.110	24
		2.662	23	1.213	25	1.155	25	1.132	25
		3.262	22	1.242	26	1.178	26	1.153	26
		4.152	21	1.271	27	1.201	27	1.174	27
		6.036	20	1.300	28	1.223	28	1.194	28
				1.328	29	1.245	29	1.214	29
				1.357	30	1.266	30	1.233	30
				1.669	40	1.462	40	1.401	40
				3.130	54	1.821	60	1.669	60
						4.450	104	2.345	120
								6.309	204
infinity	9	infinity	19	infinity	49	infinity	99	infinity	199

Abbreviations: df_C, combined degrees of freedom; PT, proficiency testing; QC, quality control; TV, target value.

Table 15C. df_C for the Combined Standard Error of the Mean and TV as a Function of the Ratio of the Standard Error of the Reference Material to the Standard Error of the Mean ($tau = se_{RM} / se_{\bar{x}}$), for Seven Runs, With Five Replicates per Run, and z = 10, 20, 50, 100, and ≥ 200 Laboratories. **NOTE:** Table 15C is intended for use in Scenarios B (PT) and C (peer group QC) in Section 3.3, when the user's experiment involves seven runs.

10 Laboratories		20 Laboratories		50 Laboratories		100 Laboratories		200 Laboratories	
tau	***df_C***	***tau***	***df_C***	***tau***	***df_C***	***tau***	***df_C***	***tau***	***df_C***
0.000	6	0.000	6	0.000	6	0.000	6	0.000	6
0.287	7	0.285	7	0.284	7	0.283	7	0.283	7
0.406	8	0.399	8	0.396	8	0.394	8	0.394	8
0.500	9	0.485	9	0.478	9	0.476	9	0.475	9
0.583	10	0.557	10	0.546	10	0.543	10	0.541	10
0.662	11	0.621	11	0.604	11	0.599	11	0.597	11
0.742	12	0.679	12	0.656	12	0.649	12	0.646	12
0.830	13	0.733	13	0.703	13	0.694	13	0.691	13
0.940	14	0.785	14	0.746	14	0.736	14	0.731	14
1.225	15	0.836	15	0.786	15	0.773	15	0.768	15
1.648	14	0.886	16	0.824	16	0.809	16	0.802	16
1.952	13	0.936	17	0.859	17	0.842	17	0.834	17
2.334	12	0.987	18	0.894	18	0.873	18	0.864	18
2.926	11	1.041	19	0.926	19	0.903	19	0.892	19
4.202	10	1.098	20	0.958	20	0.931	20	0.919	20
		1.160	21	0.989	21	0.958	21	0.945	21
		1.231	22	1.018	22	0.984	22	0.970	22
		1.316	23	1.047	23	1.009	23	0.993	23
		1.434	24	1.076	24	1.033	24	1.016	24
		1.800	25	1.104	25	1.057	25	1.038	25
		2.354	24	1.132	26	1.080	26	1.059	26
		2.787	23	1.159	27	1.102	27	1.079	27
		3.340	22	1.187	28	1.123	28	1.099	28
		4.202	21	1.214	29	1.145	29	1.118	29
		6.066	20	1.241	30	1.165	30	1.136	30
				1.528	40	1.354	40	1.300	40
				2.858	55	1.695	60	1.560	60
						4.062	105	2.201	120
								5.759	205
infinity	9	infinity	19	infinity	49	infinity	99	infinity	199

Abbreviations: df_C, combined degrees of freedom; PT, proficiency testing; QC, quality control; TV, target value.

3.6 Interpretation

If the verification interval includes the observed mean, $\bar{\bar{x}}$, bias is not statistically significant (not shown to be different from zero) within the limitations of the experiment.

To demonstrate that the experiment had sufficient precision and enough replicates to detect bias exceeding the specified allowable bias, compare the defined allowable bias to the expanded combined uncertainty (half width of the CI for the bias, $t_{0.975,df_C} \times se_C$).

If the expanded combined uncertainty exceeds the specified allowable bias, the experiment lacks sufficient data to detect clinically significant bias. More runs are necessary.

If the expanded combined uncertainty is less than the specified allowable bias, the experiment should have sufficient data to detect significant bias. However, if the duration of the experiment was only one day or two days, the true uncertainty may be very different from the estimated uncertainty. (Accordingly, this guideline recommends a study involving measurements on at least five days.) This condition is most likely to occur when the between-run SD, σ_B, is equal to or greater than the repeatability SD, σ_R. Use caution when interpreting results. σ_B can be calculated from the σ_R and σ_{WL} given in the manufacturer's PI. σ_B may also be estimated via the precision verification experiment. In any case, if σ_B is close to or exceeds σ_R, more runs may be necessary to detect bias.

If the verification interval does not include $\bar{\bar{x}}$, the estimated bias is statistically different from zero.

1. Determine whether the bias, $\bar{\bar{x}}$ – TV, is acceptable for the laboratory's needs by comparing it to the user-specified allowable bias (see Chapter 1). The bias may be statistically significant, but clinically acceptable.
2. Investigate, and, if necessary, contact the manufacturer for assistance.

NOTE 1: *DF* will be between *nRun* – 1 (ie, four in the precision experiment with five runs) and *nRep* – *nRun* (the total number of replicates minus the number of runs, ie, 20 in the precision experiment with five runs). If the within-laboratory SD is large relative to the repeatability SD, the *DF* will be low, whereas if the within-laboratory SD is approximately equal to or just slightly higher than the repeatability SD, the *DF* will be high.

NOTE 2: The upper limit of $se_{\bar{\bar{x}}}$ is $\frac{s_{WL}}{\sqrt{nRun}}$. If the calculated $se_{\bar{\bar{x}}}$ exceeds this limit, there is a calculation error.

NOTE 3: A lower limit of $se_{\bar{\bar{x}}}$ is $\frac{s_R}{\sqrt{nRep \cdot nRun}}$. A calculated $se_{\bar{\bar{x}}}$ value below this limit indicates a calculation error.

The calculation of standard errors and the verification interval should be reliable when the manufacturer of the reference material provides the uncertainty of the material's assigned value, or when the material is from a PT event, and the peer group SD and number of participants are given.

Calculation of the standard error of the assigned value of the reference material is less reliable when the material is a QC material or the peer group SD and number of laboratories are used in the calculations. A peer group's statistics can be skewed by one or more laboratories that submit many more data points than most participants. In some pools, one very large laboratory may submit half or more of the data. Such information about the peer group is not usually available to participating laboratories.

When the standard error of the reference material is assumed to be zero, the verification interval may be falsely narrow due to unknown imprecision or bias in the assigned value. The falsely narrow verification interval may lead to erroneously concluding that there is a real bias between the observed mean and the assigned mean when there is none. This situation can occur when "assayed controls" are used as the reference material and no uncertainty is provided, or when analyte concentrations have been adjusted by spiking with drugs or endogenous substances.

Some PT and QC materials do not perfectly match the matrix of native samples. This does not invalidate their use as reference materials, however, if the user laboratory is interested in assessing bias relative to peer means in order to predict PT performance (see CLSI document EP14[26]).

It is possible, in the same experiment, for bias to be undetectable with one or more of the reference materials, and for bias to be statistically significant for one or more of the other reference materials. When this occurs, compare the statistically significant biases to allowable bias. If one or more of the biases exceeds allowable bias, investigation is necessary.

IMPORTANT NOTE:

Some PT and QC materials do not perfectly match the matrix of native samples.

3.7 Worked Examples

Several hypothetical examples are provided to illustrate the calculations used in this experiment, including calculation of the verification interval from results of the precision experiment and by using the manufacturer's precision claims.

Worked Examples 1A and 1B are based on the ferritin example used in Section 2.3.10 for the precision verification study. In Worked Example 1A, the S_R and S_{WL} values calculated in Section 2.3.10 are used to calculate the verification interval. In Worked Example 1B, the manufacturer-supplied values are used. These examples demonstrate estimation of bias using PT materials and calculation of the verification interval when three samples are tested.

Worked Examples 2A and 2B are based on testing of an international reference material for albumin. In Worked Example 2A, the user-determined S_R and S_{WL} values are used to calculate the verification interval.

In Worked Example 2B, the manufacturer-supplied values are used. The verification interval is calculated assuming one sample is tested.

Worked Examples 3A and 3B are based on a user's repeated measurements of a sample spiked with digoxin up to a concentration of 2.0 µg/L. The S_{WL} / S_R ratio is 4.0 in Worked Example 3A, and 1.00 in Worked Example 3B. These examples demonstrate the estimation of bias using materials whose assigned values are assumed to have no uncertainty and infinite *DF*. The verification interval is calculated assuming two samples are tested.

Worked Example 4 is a second digoxin spiking example, this time to a concentration of 1.0 µg/L, using the manufacturer-supplied S_R and S_{WL} values. Again, the assigned value of the material is assumed to have zero standard error and infinite *DF*. The verification interval is assuming two samples are tested.

3.7.1 Worked Example 1A: Ferritin Precision Example in Section 2.3.10 Using Statistics From Precision Experiment

A PT survey sample was used in the precision example in Section 2.3.10. (Assume three samples were tested in the same experiment.) The peer group mean value for ferritin from the survey was 142.5 µg/L, the group SD was 4.5 mg/L, and there were 43 participants. The user specified an allowable bias of 10% from the peer group mean, or 14.2 µg/L.

In the user's experiment in Section 2.3.10, there were five runs with five replicates per run. From Table 10 in Section 2.3.10, the user calculated a grand mean of 140.1 mg/L, an s_R of 1.18 mg/L, and s_{WL} of 2.40 µg/L. The user's estimates of S_R and S_{WL} are used in the example calculations below.

1. Calculate the standard error of the mean:

$$se_{\bar{\bar{x}}} = \sqrt{\frac{1}{nRun}\left[s_{WL}^2 - \left(\frac{nRep-1}{nRep}\right)s_R^2\right]} = \sqrt{\frac{1}{5}\left[2.40^2 - \left(\frac{4}{5}\right)1.78^2\right]} = 0.80 \text{ µg/L}.$$

2. Calculate the standard error of the TV, as shown in Section 3.3, Scenario B, as:

$$se_{RM} = \frac{s_{RM}}{\sqrt{nLab}} = \frac{4.5 \text{ µg/L}}{\sqrt{43}} = 0.69 \text{ µg/L}.$$

3. Calculate the combined standard error of the mean and TV, se_C, as:

$$se_C = \sqrt{se_{\bar{\bar{x}}}^2 + se_{RM}^2} = \sqrt{0.80^2 + 0.69^2} = 1.06 \text{ µg/L}.$$

4. Calculate *tau* as:

$$tau = \frac{se_{RM}}{se_{\bar{\bar{x}}}} = \frac{0.69}{0.96} = 0.72.$$

5. From Table 15A, obtain df_C for 43 laboratories, with *tau* = 0.72: df_C = 9 (used table entry for 50 laboratories).

6. Obtain the value of *t* for α = 0.05 with nine *DF* and three samples:
$m = t_{1-\alpha/2,nSam,\nu} = t_{1-\alpha/6,\nu} = t_{0.9917,9} = 2.94.$

7. Calculate the verification interval:

Verification Interval = TV ± (m • se_C) = 142.5 µg/L ± (2.94 • 1.06 µg/L)
= 142.5 ± 3.12 µg/L = Verification Interval = 139.4 – 145.6 µg/L.

8. The observed mean of 140.1 mg/L is within the verification interval.

The estimate of the bias is calculated as $\bar{\bar{x}}$ – TV, 140.1 – 142.5, or –2.4 µg/L.

The observed bias of –2.4 µg/L is not statistically significant.

3.7.2 Worked Example 1B: Ferritin Precision Example in Section 2.3.10 Using Statistics From Manufacturer's Claims

A PT survey sample was used in the precision example in Section 2.3.10. (Assume three samples were tested in the same experiment.) The peer group mean value from the survey was 142.5 µg/L, the group SD was 4.5 µg/L, and there were 43 participants. The user specified an allowable bias of 10% from the peer group mean, or 14.25 µg/L.

In the user's experiment in Section 2.3.10, there were five runs with five replicates per run. The user chose to interpolate the claimed %CVs for repeatability and within-laboratory imprecision in the PI precision table at 102 µg/L and 211 µg/L to estimate the claimed precision at 140.1 µg/L. The interpolated $\%CV_R$ claim was (2.0% + 1.4%) / 2 = 1.7%. At the user's observed mean of 140.1 µg/L, S_R = 2.38 µg/L. The interpolated $\%CV_{WL}$ claim was (3.4% + 2.4%) / 2 = 2.9%. At the user's observed mean of 140.1 µg/L, the calculated claimed S_{WL} = 4.06 µg/L.

1. Calculate the standard error of the mean:

$$se_{\bar{\bar{x}}} = \sqrt{\frac{1}{nRun}\left[s_{WL}^2 - \left(\frac{nRep-1}{nRep}\right)s_R^2\right]} = \sqrt{\frac{1}{5}\left[4.06^2 - \left(\frac{4}{5}\right)2.38^2\right]} = 1.55 \text{ µg/L}.$$

2. Calculate the standard error of the TV as shown in Section 3.3, Scenario B, as:

$$se_{RM} = \frac{s_{RM}}{\sqrt{nLab}} = \frac{4.5 \text{ µg/L}}{\sqrt{43}} = 0.69 \text{ µg/L}.$$

3. Calculate the combined standard error of the mean and TV, se_C, as:

$$se_C = \sqrt{se_{\bar{\bar{x}}}^2 + se_{RM}^2} = \sqrt{1.55^2 + 0.69^2} = 1.70 \text{ µg/L}.$$

4. Calculate *tau* as:

$$tau = \frac{se_{RM}}{se_{\bar{\bar{x}}}} = \frac{0.69}{1.55} = 0.45.$$

5. From Table 15A, obtain df_C for 43 laboratories, with *tau* = 0.45: df_C = 6 (used table entry for 50 laboratories).

6. Obtain the value of *t* for α = 0.05 with six *DF*:
$m = t_{1-\alpha/2,nSam,v} = t_{1-\alpha/6,v} = t_{0.9917,6} = 3.29.$

7. Calculate the verification interval:

Verification Interval = TV ± ($m \bullet se_C$) = 142.5 µg/L ± (3.29 • 1.70 µg/L) = 142.5 ± 5.6 µg/L = Verification Interval = 136.9 – 148.1 µg/L.

8. The observed mean of 140.1 µ/L is within the verification interval.

The estimate of the bias is calculated as $\bar{\bar{x}}$ – TV, 140.1 – 142.5, or –1.4 µg/L.

The observed bias of –1.4 µg/L is not statistically significant.

3.7.3 Worked Example 2A: Testing of Albumin Reference Material Using Statistics From the Precision Experiment

An albumin measurement procedure was evaluated. An albumin certified reference material was tested over six days, one run per day, with five replicates per run. The TV for the material was 37.2 g/L, with an expanded standard uncertainty (*U*) of 1.2 g/L (*k* = 2). The observed repeatability (within-run SD) was 0.4 g/L at 3.7 g/L, and the observed within-laboratory imprecision SD was 0.6 g/L at 37.0 g/L. The user obtained a mean albumin concentration of 38.5 g/L. The user's specified allowable bias was 1.8 g/L.

1. Calculate the standard error of the mean:

$$se_{\bar{\bar{x}}} = \sqrt{\frac{1}{nRun}\left[s_{WL}^2 - \left(\frac{nRep-1}{nRep}\right)s_R^2\right]} = \sqrt{\frac{1}{6}\left[0.6^2 - \left(\frac{4}{5}\right)0.4^2\right]} = 0.2 \text{ g/L}.$$

2. Calculate the standard error of the TV, as shown in Section 3.3, Scenario A, as:

$$se_{RM} = \frac{U}{k} = \frac{1.2 \text{ µg/L}}{2} = 0.6 \text{ g/L}.$$

3. Calculate the combined standard error of the mean and TV, se_C, as:

$$se_C = \sqrt{se_{\bar{\bar{x}}}^2 + se_{RM}^2} = \sqrt{0.2^2 + 0.6^2} = 0.63 \text{ g/L}.$$

4. Calculate $df_{\bar{\bar{x}}}$ as:

$df_{\bar{\bar{x}}} = nRun - 1 = 6 - 1 = 5.$

5. Because the reference material in this example is assumed to have infinite *DF*, calculate df_C as:

$$df_C = \left(\frac{se_C}{se_{\bar{\bar{x}}}}\right)^4 = 5\left(\frac{0.63}{0.2}\right)^4 = 5\,(3.15)^4 = 5 \bullet 98.46 = 492.3.$$

6. Obtain the value of *t* for α = 0.05 with 492 *DF*:

$m = t_{1-\alpha/2,nSam,v} = t_{0.975,492} = 1.96.$

7. Calculate the verification interval:

Verification Interval = TV ± (m • se_C) = 3.72 g/L ± (1.96 • 0.63 g/L) = 37.2 g/L ± 1.2 g/L = Verification Interval = 36.0 g/L – 38.4 g/L.

8. The observed mean of 38.5 g/L is not within the verification interval.

The estimate of the bias is calculated as $\bar{\bar{x}}$ – TV, 38.5 g/L – 37.2 g/L, or 1.3 g/L.

The observed bias of 1.3 g/L is statistically significant. However, the bias is acceptable because it is less than the user's defined allowable bias of 1.8 g/L.

3.7.4 Worked Example 2B: Testing of Albumin Reference Material Using Statistics From the Manufacturer's Claims

An albumin measurement procedure was evaluated. An albumin certified reference material was tested over six days with five replicates per run. The TV for the material was 37.2 g/L, with an expanded standard uncertainty (U) of 1.2 g/L (k = 2). The manufacturer's claimed repeatability (within-run SD) was 0.3 g/L at 37.0 g/L, and the manufacturer's claimed within-laboratory imprecision SD was 0.5 g/L at 37.0 g/L. The user obtained a mean albumin concentration of 38.5 g/L. The user's specified allowable bias was 2.0 g/L.

1. Calculate the standard error of the mean:

$$se_{\bar{\bar{x}}} = \sqrt{\frac{1}{nRun}\left[s_{WL}^2 - \left(\frac{nRep-1}{nRep}\right)s_R^2\right]} = \sqrt{\frac{1}{6}\left[0.5^2 - \left(\frac{4}{5}\right)0.3^2\right]} = 0.17 \text{ g/L}.$$

2. Calculate the standard error of the TV, as shown in Section 3.3, Scenario A, as:

$$se_{RM} = \frac{U}{k} = \frac{1.2 \text{ g/L}}{2} = 0.6 \text{ g/L}.$$

3. Calculate the combined standard error of the mean and TV, se_C, as:

$$se_C = \sqrt{se_{\bar{\bar{x}}}^2 + se_{RM}^2} = \sqrt{0.17^2 + 0.6^2} = 0.62 \text{ g/L}.$$

4. Calculate $df_{\bar{\bar{x}}}$ as:

$df_{\bar{\bar{x}}} = nRun - 1 = 6 - 1 = 5.$

5. Calculate df_C as:

$$df_C = df_{\bar{\bar{x}}} \bullet \left(\frac{se_C}{se_{\bar{\bar{x}}}}\right)^4 = 5\left(\frac{0.62}{0.17}\right)^4 = 5\,(3.15)^4 = 5 \bullet 177 = 885.$$

6. Obtain the value of t for $\alpha = 0.05$ with 885 *DF* (ie, essentially infinite *DF*):

$m = t_{1-\alpha/2,nSam,v} = t_{0.975,885} = 1.96.$

7. Calculate the expanded combined standard error:

   $m \cdot se_C = 1.96 \cdot 0.62$ g/L = 1.2 g/L.

8. Calculate the verification interval:

   Verification Interval = TV ± $(m \cdot se_C)$ = 37.2 g/L ± 1.2 g/L = 36.0 g/L – 38.4 g/L.

9. The observed mean of 38.5 g/L is not within the verification interval.

   The estimate of the bias is calculated as $\bar{\bar{x}}$ – TV, 38.5 g/L – 37.2 g/L, or 1.3 g/L.

   The observed bias of 1.3 g/L is statistically significant, but acceptable because it is less than the user's defined allowable bias of 2.0 g/L.

3.7.5 Worked Example 3A: Testing of Sample Spiked With Digoxin Using Statistics From the Precision Experiment (Extremely High s_{WL}/ s_R)

A drug-free serum sample was spiked with digoxin up to a concentration of 2.0 µg/L. The sample was tested on five days, with one run per day, with five replicates per run. Two samples were tested in the same experiment. The user's observed repeatability (within-run SD) was 0.01 µg/L, and the within-laboratory precision SD was 0.04 µg/L. The user obtained a mean digoxin concentration of 1.97 µg/L. The user's specified allowable bias was 0.1 µg/L.

1. Calculate the standard error of the mean:

$$se_{\bar{\bar{x}}} = \sqrt{\frac{1}{nRun}\left[s_{WL}^2 - \left(\frac{nRep-1}{nRep}\right)s_R^2\right]} = \sqrt{\frac{1}{5}\left[0.04^2 - \left(\frac{4}{5}\right)0.1^2\right]} = 0.0174 \text{ g/L}.$$

2. The standard error of the TV is assumed to be zero.

   $se_{RM} = 0$ µg/L.

3. Calculate the combined standard error of the mean and TV, se_C, as:

   $se_C = se_{\bar{\bar{x}}} = 0.0174$ µg/L.

4. Calculate $df_{\bar{\bar{x}}}$ as:

   $df_{\bar{\bar{x}}} = nRun - 1 = 5 - 1 = 4$.

5. df_C is simply $df_{\bar{\bar{x}}}$.

   $df_C = 4$

6. Obtain the value of t for $\alpha = 0.05$ with four *DF:*

   $t_{1-\alpha/2,nSam,v} = m = t_{1-\alpha/4,v} = t_{0.9875,4} = 3.50$.

7. Calculate the expanded combined standard error:

   $m \cdot se_C = 3.50 \cdot 0.0174$ µg/L = 0.061 µg/L.

8. Calculate the verification interval:

   Verification Interval = TV ± $(k \cdot se_C)$ = 2.00 µg/L ± 0.061 µg/L = 1.94 µg/L – 2.06 µg/L.

9. The observed mean of 1.97 µg/L is within the verification interval.

The estimate of the bias is calculated as $\bar{\bar{x}} - \text{TV}$, 1.97 µg/L − 2.00 µg/L, or −0.03 µg/L.

The observed bias of 0.03 µg/L is not statistically significant.

3.7.6 Worked Example 3B: Testing of Sample Spiked With Digoxin Using Statistics From the Precision Experiment (Extremely Low s_{WL} / s_R)

A drug-free serum sample was spiked with digoxin up to a concentration of 2.0 µg/L. The sample was tested on five days, with one run per day, with five replicates per run. Two samples were tested in the same experiment. The user's observed repeatability (within-run SD) was 0.04 µg/L, and the within-laboratory imprecision SD was 0.04 µg/L. The user obtained a mean digoxin concentration of 1.96 µg/L. The user's specified allowable bias was 0.1 µg/L.

1. Calculate the standard error of the mean:

$$se_{\bar{\bar{x}}} = \sqrt{\frac{1}{nRun}\left[s_{WL}^2 - \left(\frac{nRep-1}{nRep}\right)s_R^2\right]} = \sqrt{\frac{1}{5}\left[0.04^2 - \left(\frac{4}{5}\right)0.04^2\right]} = 0.008 \text{ µg/L}.$$

2. The standard error of the TV is assumed to be zero.

$se_C = 0$ µg/L

3. Calculate the combined standard error of the mean and TV, se_C, as:

$se_C = se_{\bar{\bar{x}}} = 0.008$ µg/L.

4. Calculate $df_{\bar{\bar{x}}}$ as:

$df_{\bar{\bar{x}}} = nRun - 1 = 5 - 1 = 4$.

5. df_C is simply $df_{\bar{\bar{x}}}$.

$df_C = 4$

6. Obtain the value of t for $\alpha = 0.05$ with four *DF:*

$m = t_{1-\alpha/2,nSam,v} = t_{1-\alpha/4,v} = t_{0.9875,4} = 3.50$.

7. Calculate the expanded combined standard error:

$m \cdot se_C = 3.50 \cdot 0.008$ µg/L = 0.028 µg/L.

8. Calculate the verification interval:

Verification Interval = TV ± ($m \cdot se_C$) = 2.00 µg/L ± 0.028 µg/L = 1.97 µg/L – 2.03 µg/L.

9. The observed mean of 1.96 µg/L is within the verification interval.

The estimate of the bias is calculated as $\bar{\bar{x}} - \text{TV}$, 1.96 µg/L − 2.00 µg/L, or −0.04 µg/L.

The observed bias of −0.04 µg/L is statistically significant, but is less than the user's specified allowable bias.

3.7.7 Worked Example 4: Testing of Sample Spiked With Digoxin Using Statistics From the Manufacturer's Claims

A drug-free serum sample was spiked with digoxin up to a concentration of 1.0 µg/L. The sample was tested on seven days, with one run per day, with five replicates per run. Two samples were tested in the same experiment. The manufacturer made claims for %CV for repeatability and within-laboratory imprecision of 4.81% and 1.58%, respectively, at 0.54 µg/L, and 6.48% and 1.91%, respectively, at 1.52 µg/L. The user chose to interpolate the claimed %CVs for repeatability and within-laboratory imprecision at 0.54 µg/L and 1.52 µg/L to estimate the claimed precision at 1.0 µg/L. The interpolated $\%CV_R$ claim was (4.81% + 1.58%) / 2 = 3.2%. At the spiked sample's digoxin concentration of 1.0 µg/L, s_R = 0.032 µg/L. The interpolated %CV*WL* claim was (6.48% + 1.91%) / 2 = 4.20%. At the spiked sample's digoxin concentration of 1.0 µg/L, s_{WL} = 0.042 µg/L.

The user's specified allowable bias was 0.04 µg/L.

The user observed a mean digoxin concentration of 0.94 µg/L.

1. Calculate the standard error of the mean:

$$se_{\bar{\bar{x}}} = \sqrt{\frac{1}{nRun}\left[s_{WL}^2 - \left(\frac{nRep-1}{nRep}\right)s_R^2\right]} = \sqrt{\frac{1}{7}\left[0.056^2 - \left(\frac{4}{5}\right)0.017^2\right]} = 0.02 \text{ µg/L}.$$

2. The standard error of the TV is assumed to be zero.

$se_{RM} = 0$ µg/L

3. Calculate the combined standard error of the mean and TV, se_C, as:

$se_C = se_{\bar{\bar{x}}} = 0.020$ µg/L.

4. Calculate $df_{\bar{\bar{x}}}$ as:

$df_{\bar{\bar{x}}} = nRun - 1 = 7 - 1 = 6.$

5. df_C is simply $df_{\bar{\bar{x}}}$.

$df_C = 6$

6. Obtain the value of *t* for α = 0.05 with eight *DF:*

$m = t_{1-\alpha/2,nSam,v} = t_{1-\alpha/4,v} = t_{0.9874,6} = 2.97.$

7. Calculate the expanded combined standard error:

$m \cdot se_C = 2.97 \cdot 0.020$ µg/L = 0.059 µg/L.

8. Calculate the verification interval:

Verification Interval = TV ± $(m \cdot se_C)$ = 1.00 µg/L ± 0.059 µg/L = 0.94 µg/L – 1.06 µg/L.

9. The observed mean of 0.93 µg/L is not within the verification interval.

The estimate of the bias is calculated as $\bar{\bar{x}}$ – TV, 0.93 µg/L – 1.00 µg/L, or –0.07 µg/L.

The observed bias of –0.07 µg/L exceeds the user's allowable bias. The user should investigate (possibly preparing a fresh spiked sample) and contact the manufacturer for assistance, if necessary.

Chapter 4
Conclusion

4 Conclusion

At the successful conclusion of the EP15 protocol, the user will have demonstrated that the precision of the measurement procedure in the user's laboratory is consistent with the manufacturer's claims for precision, and will have demonstrated that the measurement procedure demonstrates no significant bias (or an acceptable amount of bias) relative to the target value of the chosen reference material.

Chapter 5

Supplemental Information

This chapter includes:

- References
- Appendixes
- The Quality Management System Approach
- Related CLSI Reference Materials

References

1 CLSI. *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition.* CLSI document EP05-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.

2 CLSI. StatisPro™ [computer program]. Version 2.5. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.

3 CLSI. *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.* CLSI document EP06-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2003.

4 CLSI. *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition.* CLSI document EP17-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.

5 CLSI. *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition.* CLSI document EP28-A3c. Wayne, PA: Clinical and Laboratory Standards Institute; 2010.

6 CLSI. *Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition.* CLSI document EP09-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.

7 CLSI. *Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition.* CLSI document EP10-A3-AMD. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.

8 Krouwer JS. Setting performance goals and evaluating total analytical error for diagnostic assays. *Clin Chem.* 2002;48(6 Pt 1):919-927.

9 CLSI. *Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline.* CLSI document EP21-A. Wayne, PA; Clinical and Laboratory Standards Institute; 2003.

10 Miller JM, Astles JR, Baszler T, et al.; National Center for Emerging and Zoonotic Infectious Diseases, CDC. Guidelines for safe work practices in human and animal medical diagnostic laboratories. *MMWR Surveill Summ.* 2012;61 Suppl:1-102.

11 CLSI. *Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Fourth Edition.* CLSI document M29-A4. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.

12 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.

13 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.

14 Bureau International des Poids et Mesures (BIPM). *International Vocabulary of Metrology – Basic and General Concepts and Associated Terms* (VIM, 3rd edition, JCGM 200:2012). http://www.bipm.org/en/publications/guides/vim.html. Accessed August 15, 2014.

15 ISO. *Statistics – Vocabulary and symbols – Part 2: Applied statistics.* ISO 3534-2. Geneva, Switzerland: International Organization for Standardization; 2006.

16 IEC. *International electrotechnical vocabulary – Electrical and electronic measurements and measuring instruments.* IEC 60050-300. Geneva, Switzerland: International Electrotechnical Commission; 2001.

17 ISO. *Accuracy (trueness and precision) of measurement methods and results – Part 1: General principles and definitions.* ISO 5725-1. Geneva, Switzerland: International Organization for Standardization; 1994.

18 Garber CC, Carey RN. Evaluation of methods. In: Kaplan LA, Pesce AJ, eds. *Clinical Chemistry: Theory, Analysis, and Correlation.* 5th ed. St. Louis, MO: Mosby, Inc.; 2010:480-506.

19 Linnet K, Boyd JC. Selection and analytical evaluation of methods—with statistical techniques. In: Burtis CA, Ashwood ER, eds. *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics.* 5th ed. St. Louis, MO: Elsevier Saunders; 2012:7-48.

20 CLSI. *Training and Competence Assessment; Approved Guideline—Third Edition.* CLSI document QMS03-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.

21 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.

22 Iglewicz B, Hoaglin DC. *How to Detect and Handle Outliers.* Milwaukee, WI: ASQC Quality Press; 1993.

23 Barnett V, Lewis T. *Outliers in Statistical Data.* 3rd ed. West Sussex, UK: John Wiley & Sons Ltd.; 1994.

24 Sadler WA. Imprecision profiling. *Clin Biochem Rev.* 2008;29 Suppl 1:S33-6.

25 Sadler WA, Australasian Association of Clinical Biochemists. Variance function program (version 11.0). http://www.aacb.asn.au/professionaldevelopment/useful-tools/variance-function-program-version-110. Accessed August 15, 2014.

26 CLSI. *Evaluation of Commutability of Processed Samples; Approved Guideline—Third Edition.* CLSI document EP14-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.

Appendix A. Precision Verification Study: Experimental Designs and Missing Values

NOTE:

When sample volume is limited, **the requirement for balance may be relaxed** if the study is extended to include additional runs.

The basic 5 × 5 experimental design advocated in this guideline involves, for every sample, $k = 5$ runs, each performed on a different day, with $n = 5$ replicates per run. This is a **balanced** design, because the same number of replicates is specified for each run. Other balanced designs are equally acceptable if they involve at least as many days and at least as many degrees of freedom for repeatability, df_R. In the 5 × 5 design, $df_R = k\,(n-1) = 5\,(5-1) = 20$, increasing the number of runs, k, to 7, 10, or 20, would allow for decreasing the number of replicates per run, n, to 4, 3, or 2, respectively, while maintaining a df_R of 20 or 21. Accordingly, these and larger balanced designs are acceptable, if the runs are performed on at least five distinct days. (When sample volume is limited, the requirement for balance may be relaxed if the study is extended to include additional runs.)

A balanced design does not guarantee a balanced dataset. Individual results may go missing due to inadequate sample volume or to other documentable, nonprecision-related errors. Additional bench work may be necessary. Missing values and suppression of statistical outliers induce imbalance in the resulting datasets, thereby complicating the statistical analysis. It may be necessary to exclude an entire run from the analysis if, for example, the QC results indicate that it was a bad run ("not in control"). This exclusion will not induce imbalance—it merely requires compensating for the missing run by processing another, not necessarily on the same day, assuming there is sufficient sample volume remaining to continue the experiment.

The dataset for any given sample is acceptable if, and only if, it involves results for at least five days and a df_R of 19 or higher after exclusion of any statistical outliers. Shortfalls must be remedied by extending the study for that sample to additional runs until these two minimum requirements are met.

The user may extend the study by performing additional runs, preferably on different days—and, if necessary, with fewer (eg, two or three) replicates per run if sample volume is limited—because this will tend to improve the reliability of the estimates, especially the estimates of within-laboratory imprecision. Furthermore, when there is an apparent outlier, additional runs may yield more convincing evidence for the result's true status and/or dampen its effect on the precision estimates.

B1 Building the One-Way Analysis of Variance Table

One-way analysis of variance (ANOVA) applied to the results for a given sample in a precision verification study typically yields output like that depicted in Tables 4 and 5 (see Section 2.3.5 of this document). If software is unavailable, entries for the sum of squares (*SS*), degrees of freedom (*DF*), and mean squares (*MS*) columns must be calculated manually. Note that "sum of squares (*SS*)" is short for sum of squared deviations from the mean. The *SS* and *DF* columns simply provide the numerators and denominators, respectively, of the variance-like quantities in the *MS* column.

For the sample in question, first determine the total number of results, N; the number of distinct runs, *k*; and the arithmetic average of the N results, $\bar{\bar{x}}$ (the "grand mean"). For Sample 2 in the worked example in Section 2.3.10 of this document, N = 25, *k* = 5, and $\bar{\bar{x}}$ = 140.12 µg/L, as computed from Table 8 (see Section 2.3.10).

Entries for the *SS* column can be obtained in a straightforward manner from two tables: a table with one row per **result** (such as Table 8), and another with one row per **run** (such as Table B1).

To compute SS_{total}, the total *SS*, from a listing like Table 8 (but dedicated to a single sample), adjoin a column, calling it *DM2* (deviation from the mean, squared). Row by row, compute the cell entries for *DM2* as the **square** of the difference between $\bar{\bar{x}}$ and the result, x_i, listed on that row. (For Sample 2, the 25 cell entries for *DM2*, expressed to four decimal places, are 0.0144, 1.2544, ..., 0.7744.) Then, take the sum of the N squared deviations now listed in that column. Algebraically:

$$SS_{total} = \sum_{i=1}^{N} (x_i - \bar{\bar{x}})^2 = \left(\sum_{i=1}^{N} x^2_i \right) - N\bar{\bar{x}}^2$$

The right-hand side of the expression shows an algebraically equivalent way of obtaining SS_{total} that may be less prone to round-off error. It corresponds to creating a column consisting of the squares of the results, taking the sum of these squares, and then subtracting N times the square of the grand mean.

Table B1 summarizes basic statistics at the grouping factor (ie, run) level for Sample 2: the number of results for each run and the average of the results for each run, in columns *n* and $\bar{x}$, respectively.

Table B1. Ferritin Example: Run Statistics for Sample 2

Run	*n*	$\bar{x}$	*DM2* • *n*
1	5	139.0	6.272
2	5	140.8	2.312
3	5	138.2	18.432
4	5	142.8	35.912
5	5	139.8	0.512

Between: *SS1* = 63.44

Appendix B. (Continued)

To compute *SS1,* the between-run *SS,* from Table B1, adjoin a column, calling it *DM2 • n,* as shown. Compute the entry for any given row in this column as the difference between $\bar{\bar{x}}$ and the run average, $\bar{x}_j$, listed on that row, with the difference squared and then multiplied by the number of results for that run, namely n_i. *SS1* is the sum of the *k* entries in the column. Algebraically:

$$SS1 = \sum_{i=1}^{k} n_i (\bar{x}_i - \bar{\bar{x}})^2 = \left(\sum_{i=1}^{k} n_i \bar{x}_i^2 \right) - N\bar{\bar{x}}^2$$

The right-hand side of the expression shows an algebraically equivalent way of obtaining *SS1*. For the balanced case (where n_i are all the same), this simplifies to:

$$SS1 = n \sum_{i=1}^{k} (\bar{x}_i - \bar{\bar{x}})^2$$

SS2, the within-run *SS,* can be obtained by subtraction from the two *SS* already computed. Alternatively, it could be computed by summing up the squared deviations of each result from its run mean:

$$SS2 = SS_{total} - SS1 = \sum_{i=1}^{k} \sum_{j=1}^{n_j} (\bar{x}_i - x_{ij})^2$$

For Sample 2, *SS1* = 63.44, *SS2* = 63.20, and SS_{total} = 126.64, as shown in Table 5 (see Section 2.3.5 of this document).

Using N and *k,* calculate the entries for the *DF* column as follows, again taking advantage of the fact that the first two entries must add up to the third:

$DF_{total} = N - 1$

$DF1 = k - 1$

$DF2 = DF_{total} - DF1 = (N - 1) - (k - 1) = N - k$

The need to subtract 1 from N and 1 from *k* to obtain DF_{total} and *DF1,* respectively, can be ascribed to the loss of one *DF* in having to compute a mean from the data, ie, from the totality of individual results or from the run averages, respectively. Because there are *k* = 5 sets of within-run data, each requiring computation of a mean, subtracting *k* from N to obtain *DF2* makes sense on the same basis. Note that the *DF* column entries are necessarily positive integers (whole numbers).

For Sample 2, where *k* = 5 and N = 25, *DF1* = 4, *DF2* = 20, and DF_{total} = 24, as shown in Table 5 (see Section 2.3.5 of this document).

To compute the two "mean squares," simply divide the component "*SS*" by their *DF*:

$MS1 = SS1 / DF1$

$MS2 = SS2 / DF2$

For Sample 2, *MS1* = 15.86 and *MS2* = 3.16, as shown in Table 5 (see Section 2.3.5 of this document).

Appendix B. (Continued)

B2 Computing n_0

Table 3 (see Section 2.3.4.2 of this document) lists values for n_0—the "average" number of results per run—when there are five, six, or seven runs, with five replicates per run and, at most, one result missing for a given sample. For other designs, n_0 must be calculated manually. For the balanced case, where all the n_i are the same, this reduces to calculating the arithmetic mean of the n_i by dividing the total number of results by the number of runs: $n_0 = n_i = N / k$. To a reasonable approximation, as can be verified from Table B3, this also holds for datasets with only a small degree of imbalance. The following computations are intended for determining n_0 precisely in the unbalanced case, but they are valid for computing n_0 in the balanced case as well.

Starting with a listing like Table B2 of the number of individual results n_i in each run, adjoin a column labeled *n2*, populating it with the squares of the n_i. (Here k and N represent the number of runs and the total number of individual results, respectively.) Compute the sum of these squares:

$$SN2 = \sum_{i=1}^{k} n_i^2$$

Then:

$$n_0 = \frac{N - \left(\frac{SN2}{N}\right)}{k - 1}$$

Table B2. Format for Precise n_0 Calculations

Balanced		
Run	n_i	*n2*
1	5	25
2	5	25
3	5	25
4	5	25
5	5	25
	k = 5	N = 25
SN2 =		125
avg.n =	5	
var.n =	0	

Unbalanced		
Run	n_i	*n2*
1	5	25
2	4	16
3	5	25
4	5	25
5	5	25
	k = 5	N = 24
SN2 =		116
avg.n =	4.8	
var.n =	0.2	

Abbreviations: *avg.n,* arithmetic mean; *var.n,* variance of the n_i.

Appendix B. (Continued)

Equivalently, using basic statistical functions, determine the arithmetic mean and (sample) variance of the n_i, calling these *avg.n* and *var.n*, respectively, as indicated beneath the table. Note that *var.n* could also be obtained as the square of the (sample) SD of the n_i. Then:

$$n_0 = avg.n - (var.n \,/\, \mathrm{N})$$

For the right side of Table B2, illustrating a relatively common unbalanced situation—the dataset is complete except for one missing or suppressed result—n_0 = (24 – [116 / 24]) / (5 – 1) = 4.7917. For the balanced situation illustrated on the left, n_0 = (25 – [125 / 25]) / (5 – 1) = 5 = n_i, as expected, because here, the number of results per run is trivially the average number of results per run. The alternative formulation yields exactly the same values: n_0 = 4.8 – (0.2 / 24) = 4.7917 for the unbalanced case, and n_0= 5 – (0.0 / 25) = 5 for the balanced case.

Table B3 provides numerical examples illustrating the effect on n_0 of missing values. Their number and distribution are relevant, but not their order.

Table B3. Examples of n_0 Calculations

n_i	N	*avg.n*	n_0	Replicates
5	25	5	5	5 5 5 5 5
5	24	4.8	4.792	5 5 5 5 4
5	23	4.6	4.587	5 5 5 4 4
5	23	4.6	4.565	5 5 5 5 3

n_i	N	*avg.n*	n_0	Replicates
6	30	5	5	5 5 5 5 5 5
6	29	4.833	4.828	5 5 5 5 5 4
6	28	4.667	4.657	5 5 5 5 4 4
6	28	4.667	4.643	5 5 5 5 5 3

Abbreviation: *avg.n*, arithmetic mean.

The two algebraically equivalent methods presented here for precisely determining n_0 represent the standard textbook approach used in one-way ANOVA for variance decomposition. Slightly different approaches have also been advocated[1] and may be implemented in off-the-shelf software, but the numerical effect of such differences is inconsequential in this context. Note that Table 3 (see Section 2.3.4.2 of this document) ignores the difference between the cases represented by the third and fourth rows in Table B3, which differ, slightly, with respect to degree of imbalance, though the number of missing values is the same.

B3 Grubbs' Factors

Table 3 (see Section 2.3.4.2 of this document) lists values for the Grubbs' factor *G*, which figures in the recommended test for statistical outliers, only for N = 23 to 25, 28 to 30, and 33 to 35. Table B4 provides a more extensive tabulation.

Appendix B. (Continued)

Table B4. Grubbs' Factors (99% Confidence Level)

N	*G*		N	*G*		N	*G*		N	*G*		N	*G*
1	N/A		21	3.031		41	3.392		61	3.567		81	3.678
2	N/A		22	3.060		42	3.404		62	3.573		82	3.682
3	1.155		23	3.087		43	3.415		63	3.580		83	3.687
4	1.496		24	3.112		44	3.425		64	3.586		84	3.691
5	1.764		25	3.135		45	3.435		65	3.592		85	3.695
6	1.973		26	3.158		46	3.445		66	3.598		86	3.700
7	2.139		27	3.179		47	3.455		67	3.604		87	3.704
8	2.274		28	3.199		48	3.464		68	3.610		88	3.708
9	2.387		29	3.218		49	3.474		69	3.616		89	3.712
10	2.482		30	3.236		50	3.482		70	3.622		90	3.716
11	2.564		31	3.253		51	3.491		71	3.627		91	3.720
12	2.636		32	3.270		52	3.500		72	3.633		92	3.724
13	2.699		33	3.286		53	3.508		73	3.638		93	3.728
14	2.755		34	3.301		54	3.516		74	3.643		94	3.732
15	2.806		35	3.316		55	3.524		75	3.648		95	3.736
16	2.852		36	3.330		56	3.531		76	3.653		96	3.740
17	2.894		37	3.343		57	3.539		77	3.658		97	3.743
18	2.932		38	3.356		58	3.546		78	3.663		98	3.747
19	2.968		39	3.369		59	3.553		79	3.668		99	3.750
20	3.001		40	3.381		60	3.560		80	3.673		100	3.754

Abbreviation: N/A, not applicable.

B4 Degrees of Freedom for Within-Laboratory Imprecision

Table 6 (see Section 2.3.6.2 of this document) lists *DF* for within-laboratory imprecision (df_{WL}) as a function of the manufacturer's claims ratio ($\rho = \sigma_{WL} / \sigma_R$), but only for experimental designs involving five to seven runs, with five replicates per run. This section describes how to calculate df_{WL} directly, and the calculations underlying Table 6 of this document.

Appendix B. (Continued)

Calculating df_{WL} Directly

The within-laboratory variance, $V_{WL} = (S_{WL})^2$, represents a **linear combination** of the variance components, namely *VB* + *VB*, extracted from a one-way ANOVA table, and df_{WL} represents the *DF* associated with this linear combination. The approach taken in this guideline relies on the widely used approximation for df_{WL} introduced by Satterthwaite.[2] It is constructed from ANOVA table elements:

- The mean squares, *MS1* and *MS2*
- The mean squares' degrees of freedom, *DF1* and *DF2*
- n_0, the "average" number of results per run

To calculate the Satterthwaite approximation from these elements, first express the within-laboratory variance estimate as a linear combination (weighted sum) of *MS1* and *MS2* from the ANOVA table, ie, in the form $a_1 MS1 + a_2 MS2$, where a_1 and a_2 are suitable weights (multipliers):

$$V_{WL} = V_W + V_B = MS2 + (MS1 - MS2) / n_0 = (1 / n_0)\, MS1 + (1 - 1 / n_0)\, MS2$$

Hence, $a_1 = 1 / n_0$ and $a_2 = 1 - 1 / n_0 = (n_0 - 1) / n_0$. The *DF* associated with *MS1* and *MS2* are, respectively, $DF1 = k - 1$ and $DF2 = N - k$, where *k* and N are the number of runs and the total number of results. For V_{WL}, the linear combination of *MS1* and *MS2*, Satterthwaite[2] argued that the following should be approximately true:

$$\frac{(a_1 MS1 + a_2 MS2)^2}{DF_{WL}} = \frac{(a_1 MS1)^2}{DF1} + \frac{(a_2 MS2)^2}{DF2}$$

This equation can be rearranged to solve for the quantity of interest, namely $df_{WL} = DF_{WL}$, for example, as $DF_{WL} = num / (den1 + den2)$, where $num = (a_1 MS1 + a_2 MS2)^2$, $den1 = (a_1 MS1)^2 / DF1$, and $den2 = (a_2 MS2)^2 / DF2$. (For Sample 2 in the ferritin example, $n_0 = 5$, $a_1 = 0.2$, $a_2 = 0.8$, $num = 32.49$, $den1 = 2.5154$, $den2 = 0.3195$, $df_{WL} = 11.46$.)

The Calculations Underlying Table 6

These calculations are based on ρ (the claims ratio, σ_{WL} / σ_R) and three elements of the user's experimental design, namely *k* (the number of runs), N (the total number of replicates), and n_0 (the "average" number of replicates per run). For a fully balanced design, the latter should be related as $n_0 = N / k$.

Set *Mean* = 1.0 and $\%CV_R = 1.0$ (arbitrary values). Then:

$$\%CV_{WL} = \rho \cdot \%CV_R.$$

Back-calculate the within-run and between-run variance components:

$$V_W = (\%CV_R \cdot Mean / 100)^2$$

$$V_{WL} = (\%CV_{WL} \cdot Mean / 100)^2$$

$$V_B = V_{WL} - V_W$$

Appendix B. (Continued)

Reconstruct the ANOVA table *MS* and *DF:*

$MS1 = V_W + n_0 \cdot V_B$

$MS2 = V_W$

$DF1 = k - 1$

$DF2 = \mathrm{N} - k$

Calculate elements of the Satterthwaite formula:

$a_1 = 1 / n_0$

$a_2 = (n_0 - 1) / n_0$

$num = (a_1 MS1 + a_2 MS2)^2$

$den1 = (a_1 MS1)^2 / DF1$

$den2 = (a_2 MS2)^2 / DF2$

Finally,

$df_{WL} = DF_{WL} = num / (den1 + den2)$

B5 Determining the Upper Verification Limit Factor, *F*

Table 7 (see Section 2.3.6.2 of this document) lists values for *F*, the upper verification limit (UVL) factor, as a function of *DF* and the number of samples, *nSam*, in the precision verification experiment, for *nSam* = 1 to 6.

To calculate the UVL factor manually, first determine *X2*, the value ("quantile" or "percentage point") for the chi-square distribution with *df* and a confidence level set at 1 – 0.05 / *nSam*, which evaluates to 95% (ie, 0.95) for *nSam* = 1 corresponding to a false rejection rate of 5% (α = 0.05)—and to 97.5%, 98.33%, 98.75%, and so on for *nSam* = 2, 3, 4, etc. (For example, in a study involving two samples, if *df* = 20, then *X2* = 34.17. Then, calculate the *UVL* factor, $F = \sqrt{X2 / df}$.

References for Appendix B

1 Burdick RK, Graybill FA. The one-fold nested design. In: Owen DB, Cornell RG, Kshirsagar AM, Kennedy WJ, Schilling EG, eds. *Confidence Intervals on Variance Components.* New York, NY: Marcel Dekker, Inc.; 1992:68-76.

2 Satterthwaite FE. Synthesis of variance. *Psychometrika.* 1941;6(5):309-316.

Appendix C. Materials With Known Concentrations

NOTE:

The organization that maintains databases of reference materials and reference measurement procedures is the **Joint Committee for Traceability in Laboratory Medicine (JCTLM).**[1] Analytes are classified by JCTLM as Type 1 if they are single, well-defined chemical entities that have the same structure in the standard, calibrant, and body fluid, and Type 2 if they are less well defined and/or are heterogeneous.

Absolute trueness of laboratory results, while assumed by some users of a laboratory service and by virtually all patients, is impossible to achieve because there will always be uncertainty. It is, however, possible to establish relative trueness in relation to a defined standard with varying degrees of certainty, depending on the kind of quantity (measurand) involved and the state of the art of its measurement. This appendix attempts to clarify some of the issues involved so as to set in context how a user may verify the trueness of a measurement procedure.

C1 Principles

Trueness of a result can only be established by reference to a standard with a defined content of the quantity (measurand). This standard may then be used to calibrate a high order reference measurement procedure (usually involving some variant of isotope dilution gas chromatography mass spectrometry), which, in turn, may be used to assign values to secondary standards in an appropriate clinically relevant matrix. Accordingly, this reference measurement procedure may be used to calibrate lower order manufacturers' comparison measurement procedures, which may be used to assign values to working calibrators in field procedures. This sequence of reference procedures and materials is known as a traceability chain, and if this chain is unbroken, end results are said to be traceable back to the standard. (The chain is broken if a noncommutable material is used). The organization that maintains databases of reference materials and reference measurement procedures is the Joint Committee for Traceability in Laboratory Medicine (JCTLM).[1] Analytes are classified by JCTLM as Type 1 if they are single, well-defined chemical entities that have the same structure in the standard, calibrant, and body fluid, and Type 2 if they are less well defined and/or are heterogeneous.

C2 Role of the Manufacturer

The manufacturer has the primary responsibility to establish trueness, using established reference measurement systems, to ensure traceability of their results. End users are utterly reliant on this responsibility being undertaken properly during the development of an assay and maintained throughout its lifetime, especially when batches of reagents change. Where an established high order reference measurement system exists, it must be used by the manufacturer. This requirement is embodied in the European Union's *in vitro* diagnostic devices directive.[2]

Appendix C. (Continued)

C3 Role of the Proficiency Testing/External Quality Assessment Service Provider

Proficiency testing/external quality assessment (PT/EQA) service providers have a key role in postmarket surveillance of assay system trueness and comparability. This role, however, may only be effective if the design of the service includes authentic, commutable materials and challenging exercises to assess important analytical characteristics such as analytical specificity, recovery of added analyte, and linearity. PT/EQA can be most effective when it employs a single validated target value (TV) for performance assessment, as use of peer group (method mean) TVs can perpetuate measurement procedure differences.

C4 Type 1 Measurands

If the measurand is a well-defined chemical entity, which is always identical in structure wherever it is encountered, assay systems can be devised that give measurement procedure–independent results that are traceable to an International System of Units (SI) definition of the measurand, usually embodied in an internationally recognized primary standard. Highly purified crystalline material may be prepared and weighed into a matrix with optimal accuracy and precision. The main uncertainties involved here are those associated with measuring volumes and masses, which can be reduced to a minimum.

Thus, for Type 1 measurands, the achievement of traceability and trueness should be a relatively straightforward matter where high order reference measurement systems exist. However, traceability and trueness of the end result of the field measurement procedure is critically dependent on the analytical specificity of the measurement procedure for the measurand. Where specificity is inadequate, accurate calibration cannot be achieved, because the system is responding to other entities. Even if the calibrants used have traceable TVs, if the detection system is nonspecific, the end result will not be traceable.

In an ideal situation, the following procedure should be in place for all Type 1 measurands:

1. Prepare and value assign a panel of unprocessed, single donation, patient sera with a wide range of endogenous analyte concentrations, including those around important clinical decision points. They should be prepared and values assigned by the established high order reference measurement procedure undertaken by a certified reference laboratory that is a member of a certified reference laboratory network.
2. Store the samples from the panels at a recognized reference materials institution.
   - An example of this arrangement is the cortisol reference panel prepared at the United Kingdom National External Quality Assessment Service Birmingham, which is lodged at the Institute for Reference Materials and Measurements in Belgium.[3]
3. Allow manufacturers to use samples of these panels in a classical split sample exercise at procedure launch and each time they make revisions to the procedure calibrants. The slope of the regression line, and scatter about the line and intercept, provide valuable information about analytical specificity, accuracy of calibration, and baseline security.
4. Publish data in PIs and on manufacturer websites in the form of regression and difference plots in an agreed standard format, so that users can compare the characteristics of measurement procedures.

Appendix C. (Continued)

If this program were in place, assay system users would have a secure knowledge base with which they might compare and assess their procedure's PT/EQA performance and that of their measurement procedure. PT/EQA providers can use the same reference measurement system to assign TVs to their materials for performance assessment rather than using peer group means, which do nothing to improve comparability. It would also provide a strong incentive for the diagnostic industry to improve trueness rather than perpetuate an unsatisfactory situation where different measurement procedures within the same company can have markedly different results.

Verification of trueness by the user for Type 1 measurands would require access to the same high order reference materials used by the manufacturer. However, for cost and commutability reasons, routine laboratories would not normally purchase these high order reference materials. They might also not be able to acquire reference panels such as those described above, because the limited volumes available would require them to be reserved for manufacturers. Nevertheless, procedures involving a variety of materials are given below. It might also be possible for laboratories to perform recovery and linearity exercises if pure measurand is available off the shelf and can be spiked into a suitable patient-like matrix. Similarly, interference exercises may be conducted. However, if a laboratory's EQA provider regularly undertakes such exercises, then the laboratory only needs to participate to gain valuable information to assess trueness.

C5 Type 2 Measurands

If the measurand is not a single, well-defined chemical entity, but is ill defined and/or heterogeneous, having different isoforms or biologically active fragments or precursors, then traceability of a result to an SI definition of the quantity is impossible. The measurand contained in a standard cannot be asserted to have the same composition as that in a biological fluid and the assay system may have different specificity for the different forms of the measurand that produce a signal in the assay system. A semantic difficulty exists here, in that one may use a name for a measurement (eg, human chorionic gonadotropin), which gives the impression to the user that a single entity exists, but this practice is misleading. A family of molecules with varying biological activity is involved, to which different assay systems will usually have varying reactivity.

For Type 2 measurands, standards are usually the World Health Organization (WHO) International Biological Reference Preparation or International Standards (IS),[4] prepared by the National Institute for Biological Standards and Control[5] in the United Kingdom. These standards are sometimes of considerable age and often impure, with TVs that have been established through a process of consensus of available field measurement procedures (often no longer in existence) with varying specificity. Unitage is usually arbitrary (eg, U/L, mU/L), although there is a trend now with the advent of recombinant materials and advanced mass spectrometry and amino acid analysis techniques to assign mass or molar values to the newer materials. High order reference measurement procedures usually do not exist and a full traceability chain cannot be established.

For Type 2 measurands, the user laboratory may be able to acquire samples of the IS from the WHO/*National Institute for Biological Standards and Control* and use them as reference materials subject to the above caveats. However, if the laboratory participates in a well-designed PT/EQA program that is routinely and regularly probing the calibration and specificity of field procedures, then there may be no need for these exercises, unless marked shifts in results indicate a quality issue.

Appendix C. (Continued)

C6 Conclusion

Whichever type of measurand is involved, and whether or not reference measurement systems exist, all stakeholders should aim to collaborate in efforts to improve trueness and comparability. It should be unacceptable for assay systems to give markedly different results for common measurands. Highly mobile populations and the emergence of electronic health care records require long-term stability and comparability of results across time and geography.

References for Appendix C

1 BIPM. JCTLM: Joint Committee for Traceability in Laboratory Medicine. http://www.bipm.org/en/committees/jc/jctlm. Accessed August 15, 2014.

2 European Parliament and the Council. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1998L0079:20120111:EN:PDF. Accessed August 15, 2014.

3 European Commission. Reference material details: ERM/IFCC-DA451. https://irmm.jrc.ec.europa.eu/rmcatalogue/detailsrmcatalogue.do?referenceMaterial=DA451%2B%2B%2B%2B%2B%2B%2B. Accessed August 15, 2014.

4 World Health Organization. WHO Expert Committee on Biological Standardization. http://www.who.int/biologicals/expert_committee/en/. Accessed August 15, 2014.

5 NIBSC. Reference materials for use in the standardisation of biological medicines. http://www.nibsc.ac.uk/products/reference_standards.aspx. Accessed August 15, 2014.

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

EP15-A3 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					
						EP09					
						EP10				EP10	
						EP14					
						EP17					
						EP21					
						EP28					
		M29									
			QMS03								

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-A3 **Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition (2014).** This document provides guidance for evaluating the precision performance of quantitative measurement procedures. It is intended for manufacturers of quantitative measurement procedures and for laboratories that develop or modify such procedures.

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.

EP09-A3 **Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition (2013).** This document addresses the design of measurement procedure comparison experiments using patient samples and subsequent data analysis techniques used to determine the bias between two *in vitro* diagnostic measurement procedures.

EP10-A3-AMD **Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition (2014).** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of a measurement procedure or device.

EP14-A3 **Evaluation of Commutability of Processed Samples; Approved Guideline—Third Edition (2014).** This document provides guidance for evaluating the commutablity of processed samples by determining if they behave differently than unprocessed patient samples when two quantitative measurement procedures are compared.

EP17-A2 **Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition (2012).** This document provides guidance for evaluation and documentation of the detection capability of clinical laboratory measurement procedures (ie, limits of blank, detection, and quantitation), for verification of manufacturers' detection capability claims, and for the proper use and interpretation of different detection capability estimates.

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, which 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.

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

Related CLSI Reference Materials (Continued)

EP28-A3c **Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (2010).** This document contains guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests.

M29-A4 **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Fourth Edition (2014).** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

QMS03-A3 **Training and Competence Assessment; Approved Guideline—Third Edition (2009).** This document provides background information and recommended processes for the development of training and competence assessment programs that meet quality and regulatory objectives.

StatisPro **StatisPro™ (2013).** This feature-rich, easy-to-use method evaluation software can be used for establishing or verifying performance characteristics of a laboratory test method. This robust statistical tool can report on precision, linearity, bias (related to trueness), comparability, reference intervals, limits of detection, and limits of quantitation based on the most up-to-date CLSI guidelines.

Active Membership (As of 1 August 2014)

Industry and Large Commercial Laboratories

Abbott (IL)
Abbott Point of Care Inc. (NJ)
AdvaMed (DC)
Aria Diagnostics (CA)
ARUP Laboratories (UT)
Astellas Pharma (IL)
AstraZeneca Pharmaceuticals (MA)
Astute Medical, Inc. (CA)
Axis-Shield PoC AS (United Kingdom [GB])
Bayer Healthcare, LLC Diagnostic Division (IN)
BD (NJ)
Beckman Coulter, Inc. (PA)
Bioanalyse, Ltd. (Turkey)
Biohit Oyj. (Finland)
BioMerieux, Inc. (MO)
Bio-Rad Laboratories, Inc. (CA)
Canon U.S. Life Sciences, Inc. (MD)
Cempra Pharmaceuticals, Inc. (NC)
Cepheid (CA)
Abbott (IL)
Abbott Point of Care Inc. (NJ)
Accelerate Diagnostics Inc. (AZ)
AdvaMed (DC)
ARH Regional Medical Center (KY)
ARUP Laboratories (UT)
Astellas Pharma (IL)
AstraZeneca Pharmaceuticals (MA)
Astute Medical, Inc. (CA)
Axis-Shield PoC AS (United Kingdom [GB])
Bayer Healthcare, LLC Diagnostic Division (KS)
BD (NJ)
Beckman Coulter (PA)
Bio-Rad Laboratories, Inc. (CA)
Bioanalyse, Ltd. (Turkey)
Biohit Oyj. (Finland)
Biomedia (Thailand) Co.,Ltd. (Thailand)
BioMerieux, Inc. (MO)
Canon U.S. Life Sciences, Inc. (MD)
Cempra Pharmaceuticals, Inc. (NC)
Cepheid (CA)
Cerexa, Inc. (CA)
Clinical Reference Laboratory (MO)
Cubist Pharmaceuticals, Inc. (MA)
Eiken Chemical Company, Ltd. (Japan)
Elanco Animal Health (IN)
EMH Regional Medical Center (OH)
Enzo Clinical Labs (NY)
Exosome Diagnostics, Inc. (MN)
Greiner Bio-One GmbH (Austria)
Greiner Bio-One Inc. (NC)
Guangzhou Daan Clinical Laboratory Center Co. Ltd (China)
Himedia Labs Ltd (India)
Hinsdale Pathology Associates (IL)
Hologic, Inc. (MA)
Icon Laboratories, Inc. (NY)
Instrumentation Laboratory (MA)
Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (NJ)
Kaiser Permanente (CA)
Laboratory Corporation of America (VA)
Life Laboratories (MA)
LifeLabs (Canada)
LifeLabs Medical Laboratory Services (Canada)
Mbio Diagnostics, Inc. (CO)
Melinta Therapeutics, Inc. (CT)
Merck & Company, Inc. (NJ)
Merial Limited & Newport Laboratories (MO)
Microbiologics (MN)
Micromyx, LLC (MI)
Myraqa, Inc. (CA)
Nihon Kohden Corporation (Japan)
Nissui Pharmaceutical Co., Ltd. (Japan)
Nova Biomedical Corporation (MA)
NovaBiotics (United Kingdom [GB])
Novartis Institutes for Biomedical Research (CA)
Ortho-Clinical Diagnostics, Inc. (NY)
Oxyrase, Inc. (OH)
PathCare Pathology Laboratory (South Africa)
PerkinElmer (Finland)
PerkinElmer Genetics, Inc. (PA)
Pfizer Inc (PA)
Phadia AB (Sweden)
Philips Healthcare Incubator (Netherlands)
QML Pathology (Australia)
Quest Diagnostics Nichols Institute (CA)
Radiometer Medical A/S (Denmark)
Roche Diagnostics Corporation (IN)
Sanofi Pasteur (PA)
Sarstedt, Inc. (NC)
Sekisui Diagnostics (MA)
Siemens Healthcare Diagnostics, Inc. (GA)
Sonic Healthcare USA (TX)
Streck Laboratories, Inc. (NE)
Sysmex America, Inc. (IL)
The Binding Site Group Ltd (United Kingdom [GB])
The Medicines Company (Canada)
Theranos (CA)
Theravance Inc. (CA)
Thermo Fisher Scientific (CA)
Thermo Scientific Microbiology Sdn Bhd (Malaysia)
Ventana Medical Systems Inc. (AZ)
Verinata Health, Inc. (CA)
Viracor-IBT Reference Laboratory (MO)
Wellstat Diagnostics, LLC (MD)
XDx, Inc. (CA)
Zoetis (MI)

Health Care Professions/Government

436 Medical Group - Dover Air Force Base (DE)
Aberdeen Royal Infirmary (United Kingdom [GB])
Academisch Ziekenhuis-VUB (Belgium)
ACL Laboratories (WI)
ACL Laboratories (IL)
ACM Medical Laboratory (NY)
Adams Memorial Hospital (IN)
Advanced Laboratory Services (PA)
Affiliated Laboratory, Inc. (ME)
AHS Morristown (NJ)
Akron Children's Hospital (OH)
Akron General Medical Center (OH)
Al Noor Hospital (United Arab Emirates)
Al Rahba Hospital (United Arab Emirates)
Alameda County Medical Center (CA)
Alaska Native Medical Center (AK)
Alaska Regional Hospital (AK)
Albany Medical Center Hospital (NY)
Alberta Health Services (Canada)
Alexandra Health Pte Ltd (Singapore)
Alfred I. du Pont Hospital for Children (DE)
All Children's Hospital (FL)
Allegiance Health (MI)
Alliance Community Hospital (OH)
Alpena Regional Medical Center (MI)
Alta Bates Summit Medical Center (CA)
Altru Health Systems (ND)
Alverno Clinical Laboratories, Inc. (IN)
American Association for Clinical Chemistry (DC)
American Association for Laboratory Accreditation (MD)
American Bio-Clinical Laboratories (CA)
American Medical Technologists (VA)
American Society for Clinical Pathology (IL)

Active Membership (As of 1 August 2014)

American Society for Microbiology (DC)
American Society of Phlebotomy Technicians (SC)
American Type Culture Collection (VA)
American University of Beirut Medical Ce (Lebanon)
Ampath (South Africa)
Anderson Cancer Center (TX)
Ann & Robert H. Lurie Children's Hospital of Chicago (IL)
Anne Arundel Medical Center (MD)
Anson General Hospital (Canada)
Appalachian Regional Healthcare System (NC)
Applied Proteomics Inc (CA)
Arhus Universitets Hospital (Denmark)
Arizona State Health Laboratory (AZ)
Arkansas Children's Hospital (AR)
Armed Forces Health Surveillance Center (AFHSC) (MD)
Arrowhead Regional Medical Center (CA)
Asan Medical Center (Korea, Republic of)
Asante Health System (OR)
Asia Pacific Regional - FHI360 (Thailand)
Asiri Group of Hospitals Ltd. (Sri Lanka)
ASPETAR (Qatar Orthopedic and Sports Medicine Hospital) (Qatar)
Aspirus Wausau Hospital (WI)
Associacao Das Pioneiras Sociais (Brazil)
Association of Public Health Laboratories (MD)
Atlantic Diagnostics Laboratories (PA)
Atlanticare Regional Medical Center (NJ)
Atrium Medical Center (OH)
Augusta Health (VA)
Aultman Hospital (OH)
Aultman North Canton Medical Foundation (OH)
Austin State Hospital (TX)
Avera McKennan Laboratory (SD)
AZ Sint-Lucas Hospital (Belgium)
Azienda Ospedale Di Lecco (Italy)
Banyan Biomarkers (CA)
Baptist Health Medical Center (FL)
Baptist Health System (TX)
Baptist Hospital Laboratory (FL)
Baptist Hospital of Miami (FL)
Baptist Memorial Health Care Corporation - Hospital Laboratories Works (TN)
Barnes-Jewish Hospital (VT)
Bassett Healthcare (NY)
Baton Rouge General (LA)
Baxter Regional Medical Center (AR)
Bay Area Hospital (OR)
Bay Medical Center (FL)
BayCare Health System (FL)
Bayfront Medical Center (FL)
Bayhealth Medical Center-Kent General Hospital (DE)
Baylor Health Care System (TX)
Baystate Medical Center (MA)
B.B.A.G. Ve U. AS., Duzen Laboratories (Turkey)
BC Centre for Disease Control (Canada)
Beaver Dam Reference Lab (WI)
Berlin Memorial Hospital (WI)
Berwick Hospital Center (PA)
Beth Goldstein Consultant (PA)
Beth Israel Deaconess Medical Center (MA)
Beth Israel Medical Center (NY)
Bethesda Memorial Hospital (FL)
Billings Clinic (MT)
Bio-Reference Laboratories (NJ)
Biodesign Institute at ASU (AZ)
Biothera, The Immune Health Company (MN)
Blanchard Valley Hospital (OH)
Blount Memorial Hospital (TN)
Blue Mountain Health System (PA)
Bon Secours Health Partners (VA)
Bon Secours Hospital (Ireland)
Boyce & Bynum Pathology Labs (MO)
Bozeman Deaconess Laboratory (MT)
Braintree Rehabilitation Hospital (MA)
Brant Community Healthcare System/Brant General Hospital (Canada)
Brazosport Regional Health System (TX)
Breathitt Veterinary Center, Murray State University (KY)
Bridgeport Hospital (CT)
Bristol Hospital (CT)
British Columbia Institute of Technology (Canada)
Brockville General Hospital (Canada)
Bronson Methodist Hospital (MI)
Broward General Medical Center (FL)
Brownwood Regional Medical Center (TX)
Bryan Medical Center (NE)
BSA Health System (TX)
Cadham Provincial Laboratory-MB Health (Canada)
California Pacific Medical Center (CA)
Cambridge Health Alliance (MA)
Campbellford Memorial Hospital (Canada)
Canadian Science Center for Human and Animal Health (Canada)
Canadian Society for Medical Laboratory Science (Canada)
Canberra Hospital (Australia)
Cape Fear Valley Medical Center Laboratory (NC)
Capital Health Regional Medical Center (NJ)
Capital Region Medical Center (MO)
Care Medics (Canada)
Carle Foundation Hospital (IL)
Carolinas Healthcare System (NC)
Carolinas Hospital System (SC)
Carpermor S.A. de C.V. (Mexico)
Carroll Hospital Center (MD)
Carteret General Hospital (NC)
Cary Medical Center (ME)
Castle Medical Center (HI)
Catholic Health Systems-Sisters of Charity Hospital (NY)
Catholic Medical Center (NH)
Cayuga Medical Center at Ithaca (NY)
CD Diagnostics, Inc. (PA)
Cedars-Sinai Medical Center (CA)
Cedimat Medical Center (FL)
Center for Phlebotomy Education (IN)
Centers for Disease Control and Prevention (GA)
Centers for Medicare & Medicaid Services (MD)
Central Baptist Hospital (KY)
Central Newfoundland Regional Health Center (Canada)
Central Ohio Primary Care Physicians (OH)
Central Pennsylvania Alliance Laboratory (PA)
Central Washington Hospital (WA)
Centre Hospitalier Anna-Laberge (Canada)
Centre Hospitalier Lyon SUD (France)
Ceylon Hospitals Limited (Sri Lanka)
Chaleur Regional Hospital (Canada)
Chambersburg Hospital (PA)
Champlain Valley Physicians Hospital (NY)
Chesapeake General Hospital (VA)
Chester County Hospital (PA)
Chi Solutions, Inc. (MI)
Children's Healthcare of Atlanta (GA)
Children's Hospital (AL)
Children's Hospital & Medical Center (NE)
Children's Hospital & Research Center At Oakland (CA)

Active Membership (As of 1 August 2014)

Children's Hospital Boston (MA)
Children's Hospital of Central California (CA)
Children's Hospital of Philadelphia (PA)
Children's Hospitals and Clinics (MN)
Children's Medical Center (TX)
Childrens Hospital - Kings Daughters (VA)
Childrens Hospital Los Angeles (CA)
Childrens Hospital of Wisconsin (WI)
Chino Valley Medical Center (CA)
Christiana Care Health Services (DE)
CHU-St. Justine (Canada)
Cibola General Hospital (NM)
Cincinnati Children's Hospital Medical Center (OH)
Citizens Memorial Hospital (MO)
City of Hope National Medical Center (CA)
City of Milwaukee Health Department (WI)
Cleveland Clinic (OH)
Clifton Fine Hospital (NY)
Clinica Hospital San Fernando (Panama)
Clinical Hospital Merkur (Croatia/Hrvatska)
CLMA (IL)
COLA (MD)
College of American Pathologists (IL)
College of Physicians and Surgeons of Alberta (Canada)
College of Physicians and Surgeons of Saskatchewan (Canada)
College of the North Atlantic (Canada)
College of Veterinary Medicine, Auburn University (AL)
Collingwood General & Marine Hospital (Canada)
Colorado State University (CO)
Columbia Memorial Hospital (NY)
Columbia Memorial Hospital (OR)
Commonwealth of Kentucky (KY)
Commonwealth of Virginia (DCLS) (VA)
Community College of Rhode Island-Flanagan Campus (RI)
Community Foundation of Northwest Indiana: Community Hospital (IN)
Community Hospital of the Monterey Peninsula (CA)
Community Hospitals of Williams County (OH)
Community Medical Center (MT)
Complexe Hospitalier de la Sagamie (Canada)
CompuNet Clinical Laboratories (OH)
Concord Hospital (NH)
Coney Island Hospital (NY)
Consultants Laboratory of WI LLC (WI)
Contra Costa Regional Medical Center (CA)
Cook Children's Medical Center (TX)
Cooper University Hospital (NJ)
Counties Manukau District Health Board, Middlemore Hospital (New Zealand)
Covenant Medical Center (TX)
Crozer-Chester Medical Center (PA)
CSSS Papineau/Hopital de Papineau (Canada)
CSSS St-Jerome (Canada)
Curry General Hospital (OR)
Dameron Hospital Association (CA)
Danat Al Emarat, Women and Children's Hospital (United Arab Emirates)
Darwin Health Library, NT Dept. of Health (Australia)
Daviess Community Hospital (IN)
Dayton Children's Medical Center (OH)
Deaconess Hospital Laboratory (IN)
Dean Medical Center (WI)
Delano Regional Medical Center/ Laboratory (CA)
Delaware Public Health Laboratory (DE)
Delnor Community Hospital (IL)
Denver Health Medical Center (CO)
Department of Veterans Affairs (DC)
DHHS NC State Lab of Public Health (NC)
Diagnostic Accreditation Program (Canada)
Diagnostic Center for Population & Animal Health (MI)
Diagnostic Laboratory Medicine, Inc. (MA)
Diagnostic Laboratory Services, Inc. (HI)
Diagnostic Medicine Services (Iceland)
Diagnostic Services of Manitoba (Canada)
Dialysis Clinic, Inc. Laboratory (TN)
Dimensions Healthcare System Prince George's Hospital Center (MD)
DMC University Laboratories (MI)
Docro, Inc. (CT)
Doctor's Data, Inc. (IL)
Dominican University of California (CA)
Door County Medical Center (WI)
Dr Sulaiman Al Habib Medical Group (Saudi Arabia)
Driscoll Children's Hospital (TX)
Drug Scan Inc. (PA)
DuBois Regional Medical Center (PA)
DUHS Clinical Laboratories (NC)
Duke University Medical Center (NC)
Dynacare Laboratory (WI)
DynaLIFE (Canada)
East Georgia Regional Medical Center (GA)
East Houston Regional Medical Center (TX)
East Texas Medical Center (ETMC) Henderson (TX)
East Texas Medical Center-Pittsburg (TX)
East Texas Medical Center - Tyler (TX)
Eastern Health Pathology (Australia)
Eastern Ontario Regional Laboratory Association (EORLA) (Canada)
Easton Hospital (PA)
Edgerton Hospital & Health Services (WI)
Edmonds Community College (WA)
Edward Hospital (IL)
Effingham Hospital (GA)
Emerson Hospital Laboratory (MA)
Emory University Hospital (GA)
Ephrata Community Hospital (PA)
Erie County Medical Center Corporation (NY)
Erlanger Health Systems (TN)
ESCMID (Switzerland)
Evangelical Community Hospital (PA)
Excela Health Latrobe Hospital (PA)
Exempla Lutheran Medical Center (CO)
Fairfax County Health Department (VA)
Fauquier Hospital (VA)
Fayette County Memorial Hospital (OH)
Federal Medical Center (MN)
Federal Medical Center Lexington (KY)
Firelands Regional Medical Center (OH)
Fisher-Titus Memorial Hospital (OH)
Fletcher Allen Health Care (VT)
Fleury S.A. (Brazil)
Floyd Memorial Hospital (IN)
Forrest General Hospital (MS)
Fort Defiance Indian Hospital (AZ)
Franklin Memorial Hospital (ME)
Fresno Community Hospital & Medical Center (CA)
Fundacao Faculdade de Medicina (Brazil)
Fundacion Mexicana Para la Salud Capitulo Peninsular A.C. (Mexico)
Gamma-Dynacare Laboratories (Canada)
Garden City Hospital (MI)
Genesis Healthcare System (OH)
Genesis Medical Center (IL)
Genome DX (Canada)
Genova Diagnostic Laboratory (NC)
George Mason University (VA)

Active Membership (As of 1 August 2014)

German Society of Allergy and Clinical Immunology (DGAKI) (Germany)
Ghent University Hospital (Belgium)
Glasgow Royal Infirmary (United Kingdom [GB])
Good Samaritan Hospital (IN)
Good Samaritan Hospital Medical Center (NY)
Grana S.A. (TX)
Grand River Hospital (Canada)
Grays Harbor Community Hospital (WA)
Great Plains Regional Med. Ctr. (NE)
Greater Lowell Pediatrics (MA)
Grey Bruce Regional Health Center (Canada)
Group Health Cooperative (WA)
Grove City Medical Center (PA)
Guelph General Hospital (Canada)
Gunnison Valley Hospital (CO)
Guthrie Clinic Laboratories (PA)
H. Lee Moffitt Cancer Center (FL)
Halton Healthcare Services (Canada)
Hamad Medical Corp-DLMP LAB QM (Qatar)
Hamilton Regional Laboratory Medicine Program - St. Joseph's (Canada)
Hannibal Regional Hospital (MO)
Hanover General Hospital (PA)
Hardin Memorial Hospital (KY)
Hardy Diagnostics (CA)
Harford Memorial Hospital (MD)
Harris Methodist HEB Hospital (TX)
Harris Methodist Hospital Southwest (TX)
Hartford Hospital (CT)
Hawaii State Hospital (HI)
HCA (TN)
Healdsburg District Hospital (CA)
Health City Cayman Islands (Cayman Islands)
Health Canada (Canada)
Health Network Lab (PA)
Health Sciences North (Canada)
Heartland Health (MO)
Helen Hayes Hospital (NY)
Hendrick Regional Laboratory (TX)
Hendricks Regional Health (IN)
Hendry Regional Medical Center (FL)
Henry Ford Hospital (MI)
Henry M. Jackson Foundation for the Advancement of Military Medicine-MD (MD)
Henry M. Jackson Foundation-Brook Army Medical Ctr (BAMC) (TX)
Hera General Hospital (Saudi Arabia)
Hiawatha Community Hospital (KS)
Highlands Medical Center (AL)
Hill Country Memorial Hospital (TX)
Hillcrest Medical Center (OK)
Hoag Memorial Hospital Presbyterian (CA)
Holstebro Hospital (Denmark)
Holy Name Hospital (NJ)
Holy Redeemer Hospital & Medical Center (PA)
Holy Spirit Hospital (PA)
Holzer Health System (OH)
Hong Kong Accreditation Service Innovation and Technology Commission (Hong Kong)
Hong Kong Sanatorium & Hospital (Hong Kong)
Hopital Charles Lemoyne (Canada)
Hopital Cite de La Sante De Laval (Canada)
Hopital de Granby-CSSS Haute-Yamaska (Canada)
Hopital du Haut-Richelieu (Canada)
Hopital Maisonneuve-Rosemont (Canada)
Hopital Santa Cabrini Ospedale (Canada)
Horizon Health Network (Canada)
Hospital Albert Einstein (Brazil)
Hospital Italiano Laboratorio Central (Argentina)
Hospital Sacre-Coeur de Montreal (Canada)
Hotel Dieu Grace Hospital Library (Canada)
Houston Medical Center (GA)
Hunt Regional Healthcare (TX)
Hunterdon Medical Center (NJ)
Huntington Memorial Hospital (CA)
Huntsville Memorial Hospital (TX)
Hutchinson Clinic, P.A. (KS)
Hutt Valley Health District Health Board (New Zealand)
IDEXX Reference Laboratories (Canada)
Imelda Hospital (Belgium)
Indiana University Health Bloomington Hospital (IN)
Industrial Technology Research Institute (ITRI) (Taiwan)
INEI-ANLIS Dr. C. G. Malbráin (Argentina)
Ingalls Hospital (IL)
Institut National de Sante Publique du Quebec (Canada)
Institute Health Laboratories (PR)
Institute of Tropical Medicine Dept. of Clinical Sciences (Belgium)
Institute of Veterinary Bacteriology (Switzerland)
Integrated BioBank (Luxembourg)
Integrated Regional Laboratories (HCA) (FL)
Interior Health (Canada)
Intermountain Health Care Lab Services (UT)
International Accreditation New Zealand (New Zealand)
International Federation of Clinical Chemistry (Italy)
International Health Management Associates, Inc. (IL)
Iredell Memorial Hospital (NC)
Italian Society of Clinical Biochemistry and Clinical Molecular Biology (Italy)
IU Health Bedford, Inc. (IN)
Jackson County Memorial Hospital (OK)
Jackson Health System (FL)
Jackson Hospital & Clinic, Inc. (AL)
Jackson Purchase Medical Center (KY)
Jameson Memorial Hospital (PA)
Jefferson Memorial Hospital (WV)
Jefferson Regional Medical Center (PA)
Jennings American Legion Hospital (LA)
Jessa Ziekenhuis VZW (Belgium)
John D. Archbold Hospital (GA)
John F. Kennedy Medical Center (NJ)
John H. Stroger, Jr. Hospital of Cook County (IL)
Johns Hopkins Medical Institutions (MD)
Johnson City Medical Center Hospital (TN)
Jonathan M. Wainwright Memorial Veterans Affairs Medical Center (WA)
Jones Memorial Hospital (NY)
Jordan Valley Community Health Center (MO)
JPS Health Network (TX)
Kaiser Medical Laboratory (HI)
Kaiser Permanente (GA)
Kaiser Permanente (MD)
Kaiser Permanente Colorado (CO)
Kaiser Permanente Medical Care (CA)
Kaleida Health Center for Laboratory Medicine (NY)
Kalispell Regional Medical Center (MT)
Kansas Department of Health & Environment (KS)
Kansas State University (KS)
Kaohsiun Chang Gung Memorial Hospital (Taiwan)
Karmanos Cancer Institute (MI)
Karolinska University Hospital (Sweden)
KCHL St. Elisabeth Hospital (Netherlands)
Keck Hospital of USC (CA)
Keelung Chang Gung Memorial Hospital (Taiwan)

Active Membership (As of 1 August 2014)

Kenora-Rainy River Regional Laboratory Program (Canada)
Kenya Medical Laboratory Technicians and Technologists Board (KMLTTB)
Kindred Healthcare (KY)
King Abdulaziz Hospital (Saudi Arabia)
King Fahad Specialist Hospital-Dammam, K.S.A. (Saudi Arabia)
King Faisal Specialist Hospital & Research Center (Saudi Arabia)
King Hussein Cancer Center (Jordan)
Kingston General Hospital (Canada)
KK Women's & Children's Hospital (Singapore)
Kuwait Cancer Control Center (Kuwait)
La Rabida Childrens Hospital (IL)
Lab Medico Santa Luzia LTDA (Brazil)
LABIN (Costa Rica)
Labor Stein + Kollegen (Germany)
Laboratoire National de Sante Publique (Haiti)
Laboratorio Bueso Arias (Honduras)
Laboratorio Clinico Amadita P. de Gonzales S.A. (DR)
Laboratorio de Referencia (FL)
Laboratorio Medico De Referencia (Colombia)
Laboratory Alliance of Central New York (NY)
Laboratory for Medical Microbiology and Infectious Diseases (Netherlands)
Laboratory Medicin Dalarna (Sweden)
Laboratory of Clinical Biology Ziekenhuis Oost-Limburg (ZOL) (Belgium)
LabPlus Auckland District Health Board (New Zealand)
Labrador Grenfell Health (Canada)
LAC/USC Medical Center (CA)
Lafayette General Medical Center (LA)
Lahey Hospital & Medical Center (MA)
Lake Charles Memorial Hospital (LA)
Lakeland Regional Laboratories (MI)
Lakeland Regional Medical Center (FL)
Lamb Healthcare Center (TX)
Lancaster General Hospital (PA)
Lanier Health Services (AL)
Lawrence and Memorial Hospitals (CT)
LeBonheur Children's Hospital (TN)
Legacy Laboratory Services (OR)
Leiden University Medical Center (Netherlands)
Lewis-Gale Medical Center (VA)
LewisGale Hospital Montgomery (VA)
Lexington Medical Center (SC)
Licking Memorial Hospital (OH)
LifeCare Medical Center (MN)
Lithuanian Society of Laboratory Medicine (Lithuania)
Little Company of Mary Hospital (IL)
Littleton Regional Healthcare (NH)
Lodi Health (CA)
Loma Linda University Medical Center (LLUMC) (CA)
London Health Sciences Center (Canada)
Long Beach Memorial Medical Center-LBMMC (CA)
Long Island Jewish Medical Center (NY)
Longmont United Hospital (CO)
Louisiana Office of Public Health Laboratory (LA)
Louisiana State University Medical Ctr. (LA)
Lower Mainland Laboratories (Canada)
Loyola University Medical Center (IL)
Luminex Corporation (WI)
Lutheran Hospital of Indiana Inc. (IN)
Lynchburg General (VA)
Lyndon B. Johnson General Hospital (TX)
MA Dept. of Public Health Laboratories (MA)
Mackenzie Health (Canada)
Magnolia Regional Health Center (MS)
Main Line Clinical Laboratories, Inc. Lankenau Hospital (PA)
Mammoth Hospital Laboratory (CA)
Margaret Mary Community Hospital (IN)
Margaret R. Pardee Memorial Hospital (NC)
Maria Parham Medical Center (NC)
Mariaziekenhuis vzw (Belgium)
Marion County Public Health Department (IN)
Marshall Medical Center South (AL)
Marshfield Clinic (WI)
Martha Jefferson Hospital (VA)
Martha's Vineyard Hospital (MA)
Martin Luther King, Jr./Drew Medical Center (CA)
Martin Memorial Health Systems (FL)
Mary Black Memorial Hospital (SC)
Mary Greeley Medical Center (IA)
Mary Hitchcock Memorial Hospital (NH)
Mary Washington Hospital (VA)
Massachusetts General Hospital (MA)
Mater Health Services - Pathology (Australia)
Maury Regional Hospital (TN)
Mayo Clinic (MN)
McAllen Medical Center (TX)
McCullough-Hyde Memorial Hospital (OH)
MCG Health (GA)
McGill University Health Center (Canada)
MCN Healthcare (CO)
MD Tox Laboratoires (CA)
Meadows Regional Medical Center (GA)
Med Health Services Laboratory (PA)
Medecin Microbiologiste (Canada)
Media Lab, Inc. (GA)
Medical Center Hospital (TX)
Medical Center of Central Georgia (GA)
Medical Centre Ljubljana (Slovenia)
Medical College of Virginia Hospital (VA)
Medical University Hospital Authority (SC)
Medical, Laboratory & Technology Consultants, LLC (DC)
Medlab Ghana Ltd. (Ghana)
Memorial Health System (CO)
Memorial Hermann Healthcare System (TX)
Memorial Hospital (PA)
Memorial Hospital of Texas County (OK)
Memorial Hospital of Union City (OH)
Memorial Medical Center (IL)
Memorial Regional Hospital (FL)
Memorial Sloan Kettering Cancer Center (NY)
Menonnite General Hospital (PR)
Mercy Franciscan Mt. Airy (OH)
Mercy Hospital (MN)
Mercy Hospital (IA)
Mercy Hospital of Franciscan Sisters (IA)
Mercy Hospital of Tiffin (OH)
Mercy Hospital St. Louis (MO)
Mercy Integrated Laboratories /Mercy St. Vincent (OH)
Mercy Medical Center (CA)
Mercy Medical Center (MD)
Mercy Medical Center (IA)
Mercy Medical Center (OH)
Mercy Regional Medical Center (OH)
Meritus Medical Laboratory (MD)
Methodist Dallas Medical Center (TX)
Methodist Healthcare (TN)
Methodist Hospital (TX)
Methodist Hospital Pathology (NE)
Methodist Sugarland Hospital (TX)
MetroHealth Medical Center (OH)
Metropolitan Medical Laboratory (IL)
Michigan Department of Community Health (MI)
Microbial Research, Inc. (CO)
MicroPath Laboratories. (FL)

Active Membership (As of 1 August 2014)

Mid America Clinical Laboratories (IN)
Mid Coast Hospital (ME)
Middelheim General Hospital (Belgium)
Middlesex Hospital (CT)
Midland Memorial Hospital (TX)
Midwestern Regional Medical Center (IL)
Mile Bluff Medical Center/Hess Memorial Hospital (WI)
Milford Regional Hospital (MA)
Minneapolis Community and Technical College (MN)
Minneapolis Medical Research Foundation (MN)
Minnesota Department of Health (MN)
MiraVista Diagnostics (IN)
Mission Hospitals Laboratory (NC)
Mississippi Baptist Medical Center (MS)
Mississippi Public Health Laboratory (MS)
Missouri State Public Health Laboratory (MO)
MolecularMD (OR)
Monadnock Community Hospital (NH)
Monongahela Valley Hospital (PA)
Monongalia General Hospital (WV)
Montana Department of Public Health and Human Services (MT)
Montefiore Medical Center (NY)
Morehead Memorial Hospital (NC)
Mount Nittany Medical Center (PA)
Mt. Sinai Hospital (Canada)
Mt. Sinai Hospital - New York (NY)
Mt. Sinai Hospital Medical Center (IL)
MultiCare Health Systems (WA)
Munson Medical Center (MI)
Muskoka Algonquin Healthcare (Canada)
Nacogdoches Memorial Hospital (TX)
Nanticoke Memorial Hospital (DE)
Nash General Hospital/Laboratory (NC)
National Cancer Institute (MD)
National Cancer Institute, CCR, LP (MD)
National Directorate for Medical Assistance (DNAM) (Mozambique)
National Food Institute Technical University of Denmark (Denmark)
National Health Laboratory Service C/O F&M Import & Export Services (South Africa)
National Heart Institute (Institut Jantung Negra) (Malaysia)
National Institute of Health-Maputo, Mozambique (Mozambique)
National Institute of Standards and Technology (MD)
National Pathology Accreditation Advisory Council (Australia)
National Society for Histotechnology, Inc. (MD)
National University Hospital (Singapore) Pte Ltd (Singapore)
National University of Ireland, Galway (NUIG) (Ireland)
National Veterinary Institute (Sweden)
Nationwide Children's Hospital (OH)
Naval Hospital Lemoore (CA)
NB Department of Health (Canada)
Nebraska LabLine (NE)
Netlab SA (Ecuador)
New Brunswick Community College (Canada)
New Brunswick Provincial Veterinary Laboratory (Canada)
New Dar Al Shifa Hospital - Kuwait (Kuwait)
New England Baptist Hospital (MA)
New Hampshire Public Health Labs. (NH)
New Hanover Regional Medical Center (NC)
New Lexington Clinic (KY)
New London Hospital (NH)
New Medical Centre Hospital (United Arab Emirates)
New York City Department of Health and Mental Hygiene (NY)
New York Eye and Ear Infirmary (NY)
New York Presbyterian Hospital (NY)
New York State Department of Health (NY)
New Zealand Blood Service (New Zealand)
Newark Beth Israel Medical Center (NJ)
Newborn Metabolic Screening Program/ Alberta Health Services (Canada)
Newman Regional Health (KS)
Niagara Health System (Canada)
NICL Laboratories (IL)
Ninewells Hospital and Medical School (United Kingdom [GB])
NorDx - Scarborough Campus (ME)
North Bay Regional Health Center (Canada)
North Carolina Baptist Hospital (NC)
North Colorado Medical Center (CO)
North Dakota Department of Health (ND)
North District Hospital (China)
North Kansas City Hospital (MO)
North Oaks Medical Center (LA)
North Shore Hospital Laboratory (New Zealand)
North Shore Medical Center (MA)
North Shore-Long Island Jewish Health System Laboratories (NY)
Northeast Georgia Health System (GA)
Northfield Hospital & Clinics (MN)
Northside Hospital (GA)
Northside Medical Center (OH)
Northumberland Hills Hospital (Canada)
Northwest Arkansas Pathology Associates (AR)
Norton Healthcare (KY)
Nova Scotia Association of Clinical Laboratory Managers (Canada)
Nova Scotia Community College (Canada)
NSW Health Pathology (Australia)
NSW Health Pathology, Sydney South West Pathology Service (Australia)
NTD Laboratories Inc (NY)
NW Physicians Lab (WA)
Oakton Community College (IL)
Ochsner Clinic Foundation (LA)
Oconee Memorial Hospital (SC)
Octapharma Plasma (NC)
Odense University Hospital (Denmark)
Office of Medical Services Laboratory (DC)
Ohio Department of Health Lab (OH)
Ohio State University Hospitals (OH)
Oklahoma Heart Hospital, LLC (OK)
Oklahoma State University: Center for Health Sciences (OK)
Olive View-UCLA Medical Center (CA)
Olmsted Medical Center Laboratory (MN)
Oneida Healthcare Center (NY)
Ontario Medical Association Quality Management Program-Laboratory Service (Canada)
Onze Lieve Vrouwziekenhuis (Belgium)
Orange County Community College (NY)
Orange Park Medical Center (FL)
Ordre Professionnel Des Technologistes Medicaux Du Quebec (Canada)
Oregon Health and Science University (OR)
Oregon Public Health Laboratory (OR)
Orillia Soldiers Memorial Hospital (Canada)
Orlando Health (FL)
OSF - Saint Anthony Medical Center (IL)
OSU Veterinary Diagnostic Laboratory (OR)
OU Medical Center (OK)
Overlake Hospital Medical Center (WA)
Ozarks Medical Center (MO)
PA Veterinary Laboratory (PA)
Pacific Diagnostic Laboratories (CA)

Active Membership (As of 1 August 2014)

Palmetto Baptist Medical Center (SC)
Palmetto Health Baptist Easley (SC)
Palo Alto Medical Foundation (CA)
Park Nicollet Methodist Hospital (MN)
Parkview Adventist Medical Center (ME)
Parkview Health Laboratories (IN)
Parkwest Medical Center (TN)
Parrish Medical Center (FL)
Pathgroup (TN)
Pathlab (IA)
Pathology Associates Medical Lab. (WA)
PathWest Laboratory Medicine WA (Australia)
Pavia Hospital Santurce (PR)
PeaceHealth Laboratories (OR)
Peninsula Regional Medical Center (MD)
Penn State Hershey Medical Center (PA)
Pennsylvania Dept. of Health (PA)
Pennsylvania Hospital (PA)
Peoria Tazewell Pathology Group, P.C. (IL)
PEPFAR President's Emergency Plan for AIDS Relief: PEPFAR Nigeria: Medical Laboratory Sciences Council of Nigeria
PEPFAR President's Emergency Plan for AIDS Relief: PEPFAR Tanzania: Centers for Disease Control and Prevention - Tanzania
PEPFAR President's Emergency Plan for AIDS Relief: PEPFAR Tanzania: Ministry of Health and Social Welfare - Tanzania
PEPFAR President's Emergency Plan for AIDS Relief: PEPFAR Zambia: Centers for Disease Control and Prevention - Zambia
PEPFAR President's Emergency Plan for AIDS Relief: PEPFAR Zambia: Ministry of Health - Zambia
PerkinElmer Health Sciences, Inc. (SC)
Peterborough Regional Health Centre (Canada)
PHIA Project, NER (CO)
Phlebotomy Training Specialists (CA)
Phoenix Children's Hospital (AZ)
Phoenixville Hospital (PA)
PHS Indian Hospital (MN)
Physicians Choice Laboratory Services (NC)
Physicians Laboratory & SouthEast Community College (NE)
Physicians Preferred Laboratory (TX)
Placer County Public Health Laboratory (CA)
Portneuf Medical Center (ID)
Poudre Valley Hospital (CO)
Prairie Lakes Hospital (SD)
Presbyterian/St. Luke's Medical Center (CO)
Preventive Medicine Foundation (Taiwan)
Prince of Wales Hospital (Hong Kong)
Princess Margaret Hospital (Hong Kong)
Proasecal LTD (Colombia)
ProMedica Laboratory Toledo Hospital (OH)
Providence Alaska Medical Center (AK)
Providence Everett Medical Center (WA)
Providence Health Services, Regional Laboratory (OR)
Providence Hospital (AL)
Providence St. Mary Medical Center (WA)
Provista Diagnostics (AZ)
Public Health Ontario (Canada)
Pullman Regional Hospital (WA)
Queen Elizabeth Hospital (Canada)
Queen Elizabeth Hospital (China)
Queensland Health Pathology Services (Australia)
Quest - A Society for Adult Support and Rehabilitation (Canada)
Quinte Healthcare Corporation - Belleville General (Canada)
Quintiles Laboratories, Ltd. (United Kingdom [GB])
Ramathibodi Hospital (Thailand)
Range Regional Health Services (Fairview Range) (MN)
Rapides Regional Medical Center (LA)
RCPA Quality Assurance Programs Pty Limited (Australia)
Redlands Community Hospital (CA)
Regina Qu'Appelle Health Region (Canada)
Regional Laboratory of Public Health (Netherlands)
Regional Medical Laboratory, Inc. (OK)
Rehoboth McKinley Christian Health Care Services (NM)
Renown Regional Medical Center (NV)
Research Institute of Tropical Medicine (Philippines)
Rhode Island Hospital (RI)
Rice Memorial Hospital (MN)
Ridgeview Medical Center (MN)
Riverside Community Hospital (CA)
Riverside Health System (VA)
Riverside Medical Center (IL)
Robert Wood Johnson University Hospital (NJ)
Robert Wood Johnson University Hospital Rahway (NJ)
Rochester General Hospital (NY)
Roger Williams Medical Center (RI)
Roper St. Francis Healthcare (SC)
Ross University School of Veterinary Medicine (Saint Kitts and Nevis)
Roswell Park Cancer Institute (NY)
Royal Hobart Hospital (Australia)
Royal Victoria Hospital (Canada)
Rush Copley Medical Center (IL)
Rush Health Systems (MS)
Russellville Hospital (AL)
SA Pathology at Women's and Children's Hospital (Australia)
Sacred Heart Hospital (WI)
Sacred Heart Hospital (FL)
Saddleback Memorial Medical Center (CA)
Saint Francis Hospital & Medical Center (CT)
Saint Francis Medical Center (IL)
Saint Mary's Regional Medical Center (NV)
Salem Hospital (OR)
Salisbury University (MD)
Samkwang Medical Laboratory (Korea, Republic of)
Sampson Regional Medical Center (NC)
Samsung Medical Center (Korea, Republic of)
San Angelo Community Medical Center (TX)
San Francisco General Hospital-University of California San Francisco (CA)
San Jose State University (CA)
San Juan Regional Medical Group (NM)
Sanford Health (ND)
Sanford USD Medical Center (SD)
Santa Clara Valley Health & Hospital Systems (CA)
Sarasota Memorial Hospital (FL)
Saratoga Hospital (NY)
SARL Laboratoire Caron (France)
Saskatchewan Disease Control Laboratory (Canada)
Saskatoon Health Region (Canada)
Saudi Aramco Medical (TX)
SC Department of Health and Environmental Control (SC)
Schneider Regional Medical Center (Virgin Islands [USA])
Scientific Institute of Public Health (Belgium)
Scott & White Memorial Hospital (TX)
Scripps Health (CA)
Scuola Di Specializzaaione- University Milano Bicocca (Italy)
Seattle Cancer Care Alliance (WA)
Seattle Children's Hospital/Children's Hospital and Regional Medical Center (WA)

Active Membership (As of 1 August 2014)

Sentara Healthcare (VA)
Sentinel CH SpA (Italy)
Seoul National University Hospital (Korea, Republic of)
Seton Healthcare Network (TX)
Seton Medical Center (CA)
Shands Jacksonville (FL)
Shanghai Centre for Clinical Laboratory (China)
Sharon Regional Health System (PA)
Sharp Health Care Laboratory Services (CA)
Shiel Medical Laboratory Inc. (NY)
Shore Memorial Hospital (NJ)
Shriners Hospitals for Children (OH)
Silliman Medical Center (Philippines)
SIMeL (Italy)
Singapore General Hospital (Singapore)
Singulex (CA)
Slidell Memorial Hospital (LA)
SMDC Clinical Laboratory (MN)
Sociedad Espanola de Bioquimica Clinica y Patologia Molec. (Spain)
Sociedade Brasileira de Analises Clinicas (Brazil)
Sociedade Brasileira de Patologia Clinica (Brazil)
Sonora Regional Medical Center (CA)
South Bay Hospital (FL)
South Bend Medical Foundation (IN)
South Bruce Grey Health Centre (Canada)
South County Hospital (RI)
South Dakota State Health Laboratory (SD)
South Eastern Area Laboratory Services (Australia)
South Miami Hospital (FL)
South Peninsula Hospital (AK)
South West Medical Center (KS)
Southeast Alabama Medical Center (AL)
SouthEast Alaska Regional Health Consortium (SEARHC) (AK)
Southern Health Care Network (Australia)
Southern Hills Medical Center (TN)
Southwest General Health Center (OH)
Southwestern Regional Medical Center (OK)
Sparrow Hospital (MI)
Speare Memorial Hospital (NH)
Spectra East (NJ)
St Elizabeth Hospital (WI)
St Rose Dominican Hospital (AZ)
St. Agnes Healthcare (MD)
St. Anthony Hospital (OK)
St. Anthony Shawnee Hospital (OK)
St. Antonius Ziekenhuis (Netherlands)
St. Barnabas Medical Center (NJ)
St. Clair Hospital (PA)
St. David's Medical Center (TX)
St. David's South Austin Hospital (TX)
St. Elizabeth Community Hospital (CA)
St. Elizabeth's Medical Center (NY)
St. Eustache Hospital (Canada)
St. Francis Hospital (SC)
St. Francis Hospital & Health Centers (NY)
St. Francis Medical Center (LA)
St. John Hospital and Medical Center (MI)
St. John's Hospital (IL)
St. John's Hospital (WY)
St. John's Hospital & Health Center (CA)
St. John's Regional Health Center (MO)
St. Joseph Health Center (MO)
St. Joseph Health System (CA)
St. Joseph Hospital (NH)
St. Joseph Medical Center (TX)
St. Joseph Mercy - Oakland (MI)
St. Joseph Regional Health Center (TX)
St. Joseph's Hospital & Medical Center (AZ)
St. Jude Children's Research Hospital (TN)
St. Jude Medical Center (CA)
St. Luke's Episcopal Hospital (TX)
St. Luke's Hospital (IA)
St. Luke's Hospital (MN)
St. Luke's Hospital (MO)
St. Luke's Hospital (PA)
St. Luke's Hospital at The Vintage (TX)
St. Luke's Medical Center (AZ)
St. Luke's Regional Medical Center (ID)
St. Mark's Hospital (UT)
St. Mary Medical Center (CA)
St. Mary Medical Center (PA)
St. Mary's Good Samaritan (IL)
St. Mary's Health Care System (GA)
St. Mary's Health Center (MO)
St. Mary's Healthcare (NY)
St. Mary's Hospital (CO)
St. Mary's Hospital (NJ)
St. Mary's Hospital (WI)
St. Michael's Hospital/Ministry Health Care (WI)
St. Nicholas Hospital (WI)
St. Peter's Bender Laboratory (NY)
St. Peter's Hospital (MT)
St. Rita's Medical Center (OH)
St. Rose Hospital (CA)
St. Tammany Parish Hospital (LA)
St. Thomas Hospital (TN)
St. Thomas-Elgin General Hospital (Canada)
St. Vincent's Medical Center (FL)
Stanton Territorial Health Authority (Canada)
Stat Veterinary Lab (CA)
State of Alabama (AL)
State of Washington Public Health Labs (WA)
Statens Serum Institut (Denmark)
Steward Norwood Hospital (MA)
Stillwater Medical Center (OK)
Stony Brook University Hospital (NY)
Stormont-Vail Regional Medical Ctr. (KS)
Strong Memorial Hospital (NY)
Sturgis Hospital (MI)
Summa Barberton Hospital (OH)
SUNY Downstate Medical Center (NY)
Susquehanna Health System (PA)
Sutter Health (CA)
Sutter Health Sacramento Sierra Region Laboratories (CA)
SV Biosystems (CA)
Swedish American Health System (IL)
Tahoe Forest Hospital (CA)
Taiwan Society of Laboratory Medicine (Taiwan)
Tallaght Hospital (Ireland)
Tampa General Hospital (FL)
Taranaki Medlab (New Zealand)
Tartu University Clinics (Estonia)
Tataa Biocenter (Sweden)
Temple University Hospital - Parkinson Pavilion (PA)
Tenet Healthcare (PA)
Tennessee Department of Health (TN)
Tewksbury Hospital (MA)
Texas A & M University (TX)
Texas Children's Hospital (TX)
Texas Department of State Health Services (TX)
Texas Health Harris Methodist Hospital Fort Worth (TX)
Texas Health Presbyterian Hospital Dallas (TX)
Texas Scottish Rite Hospital for Children (TX)
The Charlotte Hungerford Hospital (CT)
The Cheshire Medical Center (NH)
The Children's Mercy Hospital (MO)
The Doctor's Clinic (OR)

Active Membership (As of 1 August 2014)

The Good Samaritan Hospital (PA)
The Hospital for Sick Children (Canada)
The Korean Society for Laboratory Medicine (Republic of Korea)
The Michener Institute for Applied Health Sciences (Canada)
The Naval Hospital of Jacksonville (FL)
The Nebraska Medical Center (NE)
The Norwegian Institute of Biomedical Science (Norway)
The Permanente Medical Group, Inc. (CA)
The University of Texas Medical Branch (TX)
The University of Tokyo (Japan)
Thomas Jefferson University Hospital, Inc. (PA)
Thomas Memorial Hospital (WV)
Timmins and District Hospital (Canada)
Torrance Memorial Medical Center (CA)
Touro Infirmary (LA)
Tri-Cities Laboratory (WA)
TriCore Reference Laboratories (NM)
Trillium Health Partners Credit Valley Hospital (Canada)
Trinity Medical Center (AL)
Trinity Muscatine (IA)
Tucson Medical Center (AZ)
Tuen Mun Hospital, Hospital Authority (Hong Kong)
Tufts Medical Center (MA)
Tulane Medical Center Hospital & Clinic (LA)
Tulane University Health Sciences Center (LA)
Twin Lakes Regional Medical Center (KY)
U.S. Medical Center for Federal Prisoners (MO)
UC Davis Medical Center Department of Pathology & Laboratory Medicine (CA)
UC San Diego Health System Clinical Laboratories (CA)
UCI Medical Center (University of California, Irvine) (CA)
UCLA Medical Center (CA)
UCONN Health Center (CT)
UCSF Medical Center China Basin (CA)
UMass Memorial Medical Center (MA)
UMC of El Paso- Laboratory (TX)
UMC of Southern Nevada (NV)
Umea University Hospital (Sweden)
UNC Hospitals (NC)
United Christian Hospital (Hong Kong)
United Clinical Laboratories (IA)
United Health Services Hospital/Wilson Hospital Laboratory (NY)
United Memorial Medical Center (NY)
United States Coast Guard (NJ)
Universidad de Guadalajara (Mexico)
Universitair Ziekenhuis Antwerpen (Belgium)
University College Hospital (Ireland)
University General Hospital (TX)
University Health Network (Canada)
University Hospital (TX)
University Hospital Center Sherbrooke (CHUS) (Canada)
University Hospital of Northern BC (Canada)
University Hospitals of Cleveland (OH)
University Medical Center (TX)
University of Alabama at Birmingham (AL)
University of Alabama Hospital Laboratory (AL)
University of Arizona Medical Center (AZ)
University of Bonn (Germany)
University of California Veterinary Medical Teaching Hospital (CA)
University of Chicago Hospitals (IL)
University of Cologne Medical Center (Germany)
University of Colorado Denver, Anschutz Medical Campus (CO)
University of Colorado Hospital (CO)
University of Guelph (Canada)
University of Idaho (ID)
University of Illinois Medical Center (IL)
University of Iowa Hospitals and Clinics (IA)
University of Iowa, Hygienic Lab (IA)
University of Louisville Hospital (KY)
University of Maryland Medical System (MD)
University of Miami (FL)
University of Michigan, Department of Pathology (MI)
University of Minnesota Medical Center-Fairview (MN)
University of Missouri Hospital (MO)
University of North Carolina - Health Services (NC)
University of Oregon (OR)
University of Pennsylvania (PA)
University of Pennsylvania Health System (PA)
University of Pittsburgh Medical Center (PA)
University of Prince Edward Island Atlantic Veterinary College (Canada)
University of Rochester Medical Center (NY)
University of South Alabama Medical Center (AL)
University of Tasmania (Australia)
University of Texas Health Center (Tyler) (TX)
University of Texas Health Science Center (TX)
University of Texas Southwestern Medical Center (TX)
University of Utah Hospital & Clinics (UT)
University of Virginia Medical Center (VA)
University of Washington Medical Center (WA)
University of Wisconsin Health (WI)
UPMC Bedford Memorial (PA)
Uvalde Memorial Hospital (TX)
UZ-KUL Medical Center (Belgium)
VA (Bay Pines) Medical Center (FL)
VA (Indianapolis) Medical Center (IN)
VA (Miami) Medical Center (FL)
VA (Tampa) Hospital (FL)
VA (Tuscaloosa) Medical Center (AL)
Vail Valley Medical Center (CO)
Valley Medical Center (WA)
Vancouver Island Health Authority (SI) (Canada)
Vanderbilt University Medical Center (TN)
Vejle Hospital (Denmark)
Vernon Memorial Hospital (WI)
Via Christi Hospitals - Wichita (KS)
Vibrant America LLC (CA)
Vidant Medical Center (NC)
Virginia Mason Medical Center (WA)
Virginia Physicians, Inc. (VA)
Virtua - West Jersey Hospital (NJ)
WakeMed (NC)
Waterbury Hospital (CT)
Watson Clinic (FL)
Wayne Healthcare (OH)
Wayne Memorial Hospital (GA)
Weeneebayko General Hospital (Canada)
Weirton Medical Center (WV)
Wellstar Health Systems (GA)
Wenatchee Valley Medical Center (WA)
Wesley Medical Center (KS)
West Georgia Health Systems (GA)
West Kendall Baptist Hospital (FL)
West Shore Medical Center (MI)
West Valley Medical Center Laboratory (ID)
West Virginia University Hospitals (WV)
Westchester Medical Center (NY)
Western Healthcare Corporation (Canada)
Western Maryland Regional Medical Center (MD)
Western Missouri Medical Center (MO)
Western Reserve Hospital (OH)
Western State Hospital (VA)

Active Membership (As of 1 August 2014)

Whangarei Hospital (New Zealand)
Wheaton Franciscan Laboratories at St. Francis (WI)
Wheeling Hospital (WV)
Whitehorse General Hospital (Canada)
Whitman Hospital & Medical Center (WA)
Wickenburg Community Hospital (AZ)
William Beaumont Army Medical Center (TX)
William Osler Health Centre (Canada)
Williamson Medical Center (TN)
Winchester Hospital (MA)
Winter Haven Hospital, Inc. (FL)
Wisconsin State Laboratory of Hygiene (WI)
Women & Infants Hospital (RI)
Women's and Children's Hospital (LA)
Woodside Health Center (Canada)
World Health Organization (Switzerland)
WuXi AppTec Co., Ltd. (China)
Wyckoff Heights Medical Center (NY)
Yale New Haven Hospital (CT)
York General Health Care Services (NE)
York Hospital (PA)
Yukon-Kuskokwim Delta Regional Hospital (AK)
Yuma Regional Medical Center (AZ)

Individuals

Mohamed O Abdelhalim (Oman)
Franklin Adkinson (MD)
Park Ae Ja (Korea, Republic of)
Shana Ahmad (NY)
Fayha Ahmed (United Kingdom [GB])
Lawal Akeem (Nigeria)
Evelyn W. Akers (NY)
Ahmed M. Albarrag (Saudi Arabia)
Erika B Ammirati (CA)
Mohammed Attaelmannan (MA)
Chris Aug (CT)
Ahmed M Azaybi (Saudi Arabia)
Cary Baird (OH)
Amy Baracz (CA)
Susan Barber (NC)
Colette Batog (PA)
Joanne Becker (NY)
Nancy Behling (AZ)
Lynn Bell (IN)
Steven Bellistri (PA)
Melissa Bennett (Canada)
Dr. Lynette Y. Berkeley PhD (MD)
Ms. Lucia M. Berte MT(ASCP) SBB, DLM; CQA(ASQ) CMQ/OE (CO)
Bhaskar Bhattacharya (India)
Elma Kamari Bidkorpeh (CA)
Abbejane Blair (MA)
Dennis Bleile (CA)
Ms. Susan Blonshine RRT, RPFT, FAARC (MI)
Fran Boemer (Belgium)
Elizabeth Brown (PA)
Steven Brown (OR)
Carey-Ann Burnham (MO)
Karen Bush (IN)
Donald R Callihan (MD)
Rebecca Cameron (MS)
Ms. Natalie Campbell RT (Canada)
Sheldon Campbell (CT)
Alan T. Cariski (CA)
A. Bjoern Carle (ME)
Dr. Maria Paz Carlos DVM, PhD, MBA (MD)
Eileen Carreiro-Lewandowski (MA)
Dr. Alexis Carter MD, FCAP, FASCP (GA)
Dr. Jose B. Casals (Denmark)
Ning Cegielski (WA)
Emily Chang (VA)
Mintrude Charles-Young (Canada)
Denise Chorley (CA)
W. Gregory Cooper, LLC (TX)
William A Coughlin (VT)
Pauline Cyr (Canada)
Redintor Dagos (Philippines)
Dr. Jeff Dahlen PhD (CA)
Imelda Daniel (CA)
Saffiatou Darboe (Gambia)
Ms. Arlene Darmanie MS (Trinidad and Tobago)
Dr. Trivikram Dasu PhD (WI)
Ms. Diana R. DeHoyos MS, MT(ASCP) (TX)
Dr. Maria del Pilar Aguinaga PhD, CLDir(NCA) (TN)
N. de Jonge (Netherlands)
Anne Delaney (AZ)
Dr. Francois Depasse PharmD, MSc (France)
Narendra Desai (CA)
Dr. Edward P. Desmond PhD (CA)
Patricia Devine (MA)
Tom Dew (PA)
Ms. Diana L. Dickson MS, RAC (PA)
Donna Downs (NV)
Dr. Sherry A. Dunbar PhD (TX)
Mr. A. Paul Durham MA (CA)
Kathleen Dwyer (TX)
Pinar Eker (Turkey)
Sahar Gamil EL-Wakil (Egypt)
Dr E Elnifro (Malta)
Paulo Enrico P. Belen (Philippines)
Mike Ero (CA)
Mr. German Esparza BSc (Colombia)
Amy F, MS (NY)
Dr. William Fales (MO)
Pilar Fernandez-Calle (Spain)
Leah Ferrier (MT)
Ms. Sue Forrest (Australia)
Marcia Foxworthy (AL)
Dr. Timothy S. Frana DVM, MS, MPH, PhD (IA)
Dr. Jeff Fuller PhD, FCCM, ABMM (Canada)
Mary Lou Gantzer (DE)
Dr. Valerio M. Genta MD (VA)
Karima Ghazzaly (TX)
Marc Goldford (IN)
Merran Govendir (Australia)
Tanya Graham (SD)
Neil Greenberg (NY)
Ann M. Gronowski (MO)
Jason Gruver (IA)
Dr. Tibor Gyorfi (GA)
John F Halsey (SC)
Dr. W. Harry Hannon PhD (GA)
Syed N Hassan (NY)
Alandria Hatcher (TX)
B. Y. Hsieh (Taiwan)
Po-Ren Hsueh (Taiwan)
Mr. Darren C. Hudach (OH)
Doreene Hyatt (CO)
Anne Igbokwe (CA)
Lugard Igharo (TX)
Cathy Trumel (France)
T. S Isbell (MO)
Dr. Megan E. Jacob PhD (NC)
Ellis Jacobs (NJ)
Carlos A. Javier (FL)
Amy Jerabek (WI)
Daniel M. Johnson (IA)
Judith Johnston (CA)
Stephen Kahn (IL)
Jiesheng Kang (MA)
Nachum Kaplan (Canada)
Mr. Bob Kaplanis PBT, MT(ASCP) (AZ)
David Kasper (Austria)
Dr. Steven C. Kazmierczak PhD, DABCC, FACB (OR)

Active Membership (As of 1 August 2014)

Natalie J. Kennel (CA)
Michael Kent (OH)
Mr. Klaus M. Kjoller MSc (Denmark)
William F. Koch (MD)
Denise Kramer (OH)
Teresa Kraus (OK)
Mr. Narayan Krishnaswami MS, MBA (MO)
Martin Kroll (NJ)
Jan Krouwer (MA)
Kristi Kuper (TX)
Dr. Patrick B. Kyle PhD (MS)
Giancarlo la Marca (Italy)
Michael LaFleur (MA)
Grace Largado (CA)
Professor Szu-Hee Lee MD, PhD (Australia)
Dr. Thomas J. Lenk PhD (CA)
Sarah B Leppanen (CA)
Andrew Leung (CA)
Jacob B Levine (NJ)
Ernst Lindhout (Netherlands)
Kristian Linnet (Denmark)
Yuqing Liu (China)
Philip Lively (PA)
Mark Loch (MN)
Moushumi Lodh (India)
Brian Lubbers (KS)
Darrell Lundrigan (Canada)
Dr. Raquel Yahyaoui Macias (Spain)
Dr. Roberta Madej (CA)
Edward Mahamba (NV)
Mr. David Manalan F(ASQ), CSQE, CBA (MA)
Wilma Mangan (CA)
Linda M Mann (CA)
Adrienne Manning (CT)
Kristin M Marckel (MN)
Richard A. Marlar (OK)
Barbara Masten (NM)
Christine McRoberts (Canada)
Dr. Piet Meijer PhD (Netherlands)
Jacques F Meis (Netherlands)
Vanessa D. Mercado (Puerto Rico)
Barbara Mervin (MD)
James J. Miller (KY)
Kathryne Miskavige (ND)
Ms. Barbara Mitchell (KS)
Kristine Moraski (PA)
Yaser Morgan (NY)
Ian Morrissey (Switzerland)
Mohamed Hanafy Morsy (Saudi Arabia)
Anna Murphy (NJ)
Nombuso Ndlovu (South Africa)
Vishwanand Negi (India)
Melanie O'Keefe (Australia)
Jeffrey O'Kelley (GA)
Joseph Oduor Ochieng (Kenya)
Olajumoke Oladipo (NY)
Mr. Gregory Olsen (NE)
Ms. Margaret Ordonez Smith de Danies (Colombia)
Mr. Jan Ostrup (Finland)
Dr. Elizabeth Palavecino MD (NC)
Dr. Mark G. Papich DVM, MS (NC)
Niketankumar Patel (MI)
Ketan Patel (MD)
Dr. Deborah Payne PhD (CO)
A. K. Peer (South Africa)
Armando Perez-Cardona (FL)
David S Perlin (NJ)
Linda Perryman (GA)
Philip A Poston, PhD (VA)
Dr. Mair Powell MD, FRCP, FRCPath (United Kingdom [GB])
Nicole Procise (IN)
Dr. Mathew Putzi (TX)
Dr. Qinfang Qian MD, PhD (MA)
Albert Rabinovitch (CA)
Tawni Reller (MN)
Ms. Allison Remensperger (CA)
Dr. Robert P. Rennie PhD (Canada)
Mary Rice (CO)
Hanna Ritzen (Sweden)
Jennifer Rogers (MI)
Dr. Markus Rose DVM, PhD (Germany)
Andreas Rothstein (Colombia)
Daniel Ryan (CA)
Habib Sadat Chaudaury (Bangladesh)
Dr. Linoj Samuel PhD, D(ABMM) (MI)
Dr. Leticia J. San Diego PhD (MI)
Caroline Satyadi (CA)
Theresa Schnellman (SC)
Paul Schreckenberger (IL)
Melvin Schuchardt (GA)
Kathleen Selover (NY)
Dan Shireman (KS)
Dinah Shore Myers (NC)
Dr. Venkatakrishna Shyamala PhD (MD)
Dr. Vijay K. Singu DVM, PhD (NE)
Martha Skorczewski (IL)
Jane L. Smith (TN)
Janis F. Smith, Laboratory (MD)
Anna V. Sombong (Philippines)
Oyetunji O. Soriyan (Nigeria)
Paul D Stamper (MD)
John Stelling (MA)
Jennifer Strom (TX)
Ara Tahmassian (MA)
Len Tanaka (HI)
José Eduardo Mucito Varela (Mexico)
Michelle Vanderpool (CA)
Suresh H Vazirani (India)
Ryan A. Vicente (Qatar)
Lenin Villalta (Ecuador)
Kim Walker (CA)
Megan Waller (MD)
Dr. Hui Wang PhD (China)
Peter Warn (United Kingdom [GB])
Mr. Niels Wartenberg (MN)
Markita Weaver (MA)
Mr. Marlon A. Webb (MD)
Alice S Weissfeld (TX)
Gary Wells (TX)
Eric Whitters (PA)
Dr L.A. Nilika Wijeratne (Australia)
Bernadette Wildemore (GA)
Dr. Emily S. Winn-Deen PhD (CA)
Mr. Dennis Winsten (AZ)
William W Wood (MA)
Ms. Sheila M. Woodcock ART, MBA, FCSMLS(D) (Canada)
Ginger Wooster (WI)
Dr. Ching Ching Wu DVM, PhD (IN)
Max Wu (CA)
Dr. Shangwei Wu PhD (China)
Stanley Wu (GA)
Idris Mohammed Yahaya (Nigeria)
Patty Yates (MS)
Steven York (OH)
Atsushi Yoshida (Japan)
Michelle L. Zaharik (Canada)
Dr. Marcia L. Zucker PhD (NJ)
Kimberly Zunker (TX)

NOTES

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Explore the Latest Offerings from CLSI!

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

THE Key TO Quality™
from the Clinical and Laboratory Standards Institute (CLSI)

Power Forward with this Official Interactive Guide

Fundamentals for implementing a quality management system in the clinical laboratory.

Find Membership Opportunities

See the options that make it even easier for your organization to take full advantage of CLSI benefits and our unique membership value.

CLSI U
Laboratory Standards Education Center

Visit the CLSI U Education Center

Where we provide the convenient and cost-effective education resources that laboratories need to put CLSI standards into practice, including webinars, workshops, and more.

Shop Our Online Products

Including eCLIPSE Ultimate Access™, CLSI's cloud-based, online portal that makes it easy to access our standards and guidelines—*anytime, anywhere.*

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

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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

P: 610.688.0100 **Toll Free (US):** 877.447.1888 **F:** 610.688.0700

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

PRINT ISBN 1-56238-965-3

ELECTRONIC ISBN 1-56238-966-1