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EP14-A3

Evaluation of Commutability of Processed Samples; Approved Guideline—Third Edition

This document provides guidance for evaluating the commutability of processed samples by determining if they behave differently than unprocessed patient samples when two quantitative measurement procedures are compared.

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

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Evaluation of Commutability of Processed Samples; Approved Guideline—Third Edition

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Abstract

Clinical and Laboratory Standards Institute document EP14-A3—*Evaluation of Commutability of Processed Samples; Approved Guideline—Third Edition* was developed for manufacturers, regulators, and providers of proficiency testing or external quality assessment programs, although it is useful to clinical laboratories as well. The document helps users 1) determine whether noncommuntability is the source of unexpected results that are sometimes observed with processed samples when two quantitative measurement procedures are compared, 2) display the magnitude of the effects, and 3) ensure that laboratory performance is evaluated fairly if noncommutability is present. The suggested protocol was developed using patient samples as the standard of comparison.

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Contents

Foreword

When manufacturers of diagnostic reagents develop measurement procedures, they attempt to design them so that they will report measurand values accurately for the intended patient samples. These measurement procedures may not be designed to produce accurate results when nonpatient samples such as external quality assessment samples, proficiency testing samples, or QC samples are measured. Because such nonpatient sample matrixes typically undergo some processing and spiking of additional components, and therefore are altered in some manner, measurand results may not reflect the accuracy that would be observed for patient samples. Processed samples that recover like patient samples are called commutable, while those that do not are called noncommutable. In this document, as with its previous edition, a matrix effect is defined broadly as differing test result biases in processed samples vs patient samples due to unknown causes. The matrix effects that cause biases compared to patient samples could be correlated to differences in conditions as encompassing as the entire measurement system or as specific as a reagent lot within a single measurement system.

Biases due to matrix effects in processed samples have the potential to affect the quality of patient care by giving an incorrect impression of the accuracy of a measurement procedure. Depending on the intended use of the processed sample, the impact can range from negligible to serious. For example, a specific bias in a measuring interval verification sample set may have a different impact on the quality of patient care than the same bias in a QC sample. A measuring interval sample set matrix-related bias can directly affect the measuring interval allowed in patient sample results, whereas a QC matrix-related bias may affect the interpretation of QC results following a reagent lot change.

Overview of Changes

As with the previous edition of this document, the objective of EP14 is to provide ways to identify the presence of noncommutability so that improvements in measurement procedure specificity and fluid compatibility may be considered. For example, the beneficial outcome of the evaluation may be a change in the processed sample's matrix or its additives, with an improvement in sample commutability. The evaluation is applicable to any type of processed sample, including (but not limited to) common calibrators, trueness controls, and certified reference materials. The techniques described are also valid for testing the commutability of other samples such as measurement procedure–specific calibrators or patient samples that have been altered (eg, added preservatives or spiking material, diluted, depleted, or frozen). This guideline will be helpful in exploring differences in test material results between measurement procedures, especially when such material serves as a basis for determining measurement procedure performance.

Key Words

Analytical interference, bias, commutability, Deming regression, matrix, matrix effect

Evaluation of Commutability of Processed Samples; Approved Guideline—Third Edition

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

1.1 Scope

This guideline provides protocols that can evaluate commutability in any nonpatient processed samples when tested using quantitative measurement procedures. Such processed samples may be used for proficiency testing/external quality assessment (PT/EQA), measuring interval verification sample sets, or QC samples.

The guideline is intended to be used by developers of commercial diagnostic tests as well as laboratory-developed tests, manufacturers of measuring interval sample sets and QC samples, and PT or EQA providers. This guideline may also be useful to all clinical laboratory professionals wishing to investigate a processed sample's commutability.

EP14 is intended to assist in the education of clinical laboratorians, regulators, and diagnostic manufacturers about the commutability of processed materials, and how a sample's matrix can affect some measurand values and their interpretation (referred to as matrix effects). For example, professionals may not be warned of a matrix effect caused by the interaction of processed PT/EQA material and the measurement procedure, and therefore the data may suggest to them that erroneous patient results are being generated, when in fact the results may be acceptable. Examples of a matrix effect due to the interaction of a processed QC and certain reagent lot(s) exist in the literature.[1] Therefore, these types of effects should not be a surprise to experienced laboratory staff and should not lead to erroneous conclusions about the same effect occurring in patient samples. This guideline should assist all interested parties in not only evaluating the presence or absence of a matrix effect, but also increasing awareness that there may be different levels of risk to the quality of patient care that are dependent on the intended use of a processed matrix.

This guideline can also be used by laboratorians performing quantitative tests for a wide variety of measurands across various disciplines to understand the commutability of processed samples. This guideline does not apply to qualitative tests.

Finally, an added benefit to following the protocol is that manufacturers and PT/EQA providers should be able to provide some documentation to government or accrediting agencies on processed samples commutability to help avoid false conclusions about the adequacy of patient testing.

It should be noted that although the protocol in this document is intended to help distinguish between effects caused by measurement procedure malfunctions and those caused by use of artificial or human-based processed samples, it does not describe approaches that specifically establish the exact mechanism or reason for any observed noncommutability. This guideline does not apply to qualitative tests that supply only "yes/no" or "positive/negative" results.

Also, it should be noted that this document is not intended to be used to evaluate sample type differences, such as serum vs plasma.

1.2 Background

1.2.1 The Problem of Noncommutability

The interest in harmonization among testing results in biological fluids has grown among the medical and laboratory professional communities, as well as with the public. Regulations and standards meant to enhance the harmonization among results of the testing process are also in place. In addition, there is renewed interest on the use of EQA schemes and PT to evaluate and monitor the agreement of results for the same laboratory test when using different measurement procedures in clinical, reference, and physician's office laboratories.

Current scientific data suggest that such use of PT/EQA results is not always feasible because of matrix effects.[2] These processed materials used as PT/EQA samples sometimes do not behave like patient samples routinely analyzed in the laboratory. Biases not generally seen with fresh biological fluids are frequently seen with PT/EQA samples, QC, and materials used as common calibrators in a traceability scheme. Because of these matrix effects, evaluating laboratory performance for agreement of results for the same laboratory test among different measurement procedures using PT/EQA samples can lead to inaccurate conclusions and, potentially, inappropriate regulatory sanctions. At the very least, the documentation of a matrix effect in PT/EQA samples, but not in patient samples, goes a long way in assuring PT/EQA providers and regulatory agencies that patient care is not being affected.

Matrix effect phenomena involve the interplay of many components in analytical testing, which include (but may not be limited to) instrument design, reagent formulation, measurement principle, calibrators, the processed sample's matrix format or composition (eg, liquid or lyophilized, bovine or human based), and sample processing technique. These components may impart a constant or proportional bias in results, and with reagent lot differences may affect between-lot variation of matrix-related bias in nonpatient materials. For example, the performance characteristics of a 1% bovine serum albumin solution could be expected to differ from those of a minimally processed human serum.

This EP14 revision contains a number of modifications intended to improve the science of the evaluation process for matrix effects as well as provide guidance as to when it should be used. In EP14-A2, the data evaluation used an ordinary linear regression (OLR) for results of the measurement procedures, whereas this edition uses the Deming regression model. The previous edition of this document did not distinguish between the different intended uses of processed samples, such as PT/EQA materials vs QC materials. These differences represent varying levels of risk associated with a potential matrix effect and therefore dictate the amount of effort, if any, that must be expended to evaluate the processed samples. This topic is discussed in detail in Section 1.2.2. Finally, because a processed sample matrix may affect other parameters, such as imprecision, a user of the previous edition may also notice that the title has changed from *Evaluation of Matrix Effects on Commutability of Processed Samples* to *Evaluation of Commutability of Processed Samples*.

The process to evaluate a nonpatient reference material's commutability is covered in CLSI document EP30[3] along with an assessment of homogeneity and stability (important attributes for reference samples). CLSI document EP30[3] also details a technique enabling manufacturers of certified reference material to test their materials' commutability with respect to multiple measurement procedures simultaneously. EP14, on the other hand, concentrates on a simplified technique to determine commutability of nonreference materials such as PT/EQA, measuring interval assessment, and QC samples. However, its technique can also be used by an *in vitro* diagnostic manufacturer to assure the commutability of measurement-specific calibrators (see CLSI document EP32[4]) or to determine whether altered patient samples (eg, added preservatives or spiking material, diluted, depleted, or frozen) can be used in studies to mimic the behavior of patient samples.

1.2.2 Risk Due to a Matrix Effect Based on Intended Use of a Processed Sample

Noncommutability attributed to a particular processed sample, depending on the intended use either for PT/EQA, measuring interval sample sets, or QC, can have different levels of risk in causing incorrect patient laboratory test results.

The clinical consequence of an analytical bias depends on several factors, such as the direction and magnitude of the bias and the analyte, which can lead to the misclassification of risk and inappropriate therapy for a patient based on the measurement. Assessment of performance of a measurement procedure using noncommutable materials can cause erroneous conclusions regarding the analytical bias and thus may cause incorrect results for patient samples if adjustments are made based on inappropriate data.

PT/EQA samples may have measurand values assigned using reference measurement procedures or by an all procedures mean value, or by the mean of selected measurement procedures. In such situations, failure to provide the expected results when PT/EQA samples are tested suggests that the measurement procedure is biased and may lead to a lengthy investigation. If this perceived bias is actually due to the noncommutability of the PT/EQA samples, then this investigation was unwarranted and potential recalibrations or other measures taken will, at best, cause delays in providing patient results and at worst cause additional uncertainty in these results.

Measuring interval verification sample sets are composed of different mixtures of a high concentration sample and a low concentration sample that creates a sample set with defined proportional relationships for measurand concentrations. Such sets are used to verify that a measurement procedure reports results in proportion to the measurand's concentration. As with the PT/EQA samples, measuring interval verification sample sets must be stable through shipping and storage by maintaining their measurand concentration. To achieve this stability, nonpatient matrixes may be used, recombinant analytes may be used to achieve specific concentrations, preservatives may be added, or other modifications may be made. Any of these processes may result in noncommutability in these samples, which, in turn, can result in a measurement procedure failing a measuring interval verification study. Again, a lengthy investigation may inappropriately ensue, causing delays in patient results or increased uncertainty in these results.

In either of these two scenarios, the risk is high that laboratory function can be disrupted because such studies are often required for continued laboratory accreditation. Therefore, such disruptions caused by noncommutability of these external samples can be prevented if the commutability of the samples is first tested per the techniques described in this guideline before they are used for such an important function. Such testing will also protect against the less likely scenario in which one of these studies passes because of noncommutability, when it should have failed.

Laboratories receive QC material with values assigned by their manufacturers. In some cases, the values may be assigned with the same measurement procedure used in the laboratory. In any case, the assigned values can be different than what the laboratory measures on its specific instrument due to the noncommutability of the samples. Erroneous interpretation can be prevented by laboratories assigning

their own expected values during acceptance testing. The values for these samples are then used to monitor the performance of the measurement procedure over time. Examples of improper applications of a noncommutable QC material include acceptance of new reagent lots (see CLSI document EP26[5]) or comparisons between measurement procedures (see CLSI documents EP09[6] and EP15[7]). In these situations, only patient samples should be used. EP14 techniques can be used to show that such cautions are warranted or to validate that a particular processes material is suitable for a stated use with a particular measurement procedure.

Manufacturers use numerous types of samples during the course of assay development and manufacture. An early task is the creation of working calibrators and product calibrators (see CLSI document EP32[4]). Many considerations regarding the stability of matrix and analyte may drive manufacturers to use nonpatient material in calibrator formulations. The decision whether to strive for commutability or to measure and adjust for the bias created by noncommutability can be informed by the techniques in this guideline.

Finally, any time a sample derived from a patient sample can be seen as potentially different from a fresh patient sample, such as a pool of individual samples, its commutability can be checked by a commutability study. For example, CLSI document EP09[6] mentions using caution when using spiked, depleted, or diluted samples. The reason for this warning is that such treatments can change patient samples' commutability. Some samples may be altered to ensure they can be used over time for a specific function. Examples include adding preservatives or freezing the samples. The effects of such alterations can be quantified by performing a measurement procedure comparison of altered vs unaltered samples per CLSI document EP09[6] or, if it is desired to use such samples in commutability studies, their commutability can be checked through EP14 techniques.

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 features 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.[8] 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.[9]

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

accuracy (measurement) – closeness of agreement between a measured quantity value and a true quantity value of a measurand (JCGM 200:2012)[10]; **NOTE 1:** The concept "measurement accuracy" is not a quantity and is not given a numerical quantity value. A measurement is said to be more accurate when it offers a smaller measurement error (JCGM 200:2012)[10]; **NOTE 2:** The term "measurement accuracy" should not be used for "measurement trueness" and the term "measurement precision" should not be used for "measurement accuracy," which, however, is related to both these concepts (JCGM 200:2012)[10]; **NOTE 3:** "Measurement accuracy" is sometimes understood as closeness of agreement between measured quantity values that are being attributed to the measurand (JCGM 200:2012)[10]; **NOTE 4:** "Accepted reference value" may be used in place of "true value"; **NOTE 5:** "Measurement accuracy" is inversely related to "measurement error" and "measurement uncertainty," and directly related to "measurement precision."

bias (of measurement) – estimate of a systematic measurement error (JCGM 200:2012). [10]

calibration – operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication (JCGM 200:2012) [10]; **NOTE:** According to the US Code of Federal Regulations, calibration is the process of testing and adjusting an instrument or test system to establish a correlation between the measurement response and the concentration or amount of the substance that is being measured by the test procedure (42 CFR 493.2).[11]

commutability (of a material) – property of a given reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two measurement procedures, and the relation obtained among the measurement results for other specified materials (ISO 15194).[12]

Deming regression – a method to estimate slope and intercept parameters from a measurement procedure comparison experiment with allowance for both measurement procedures to have imprecision; **NOTE:** The measurement error for each measurement procedure is accounted for in the estimation procedure (see CLSI document EP09).[6]

heteroscedasticity – changes in the variability of a measurement procedure due to changes in the measurand level; **NOTE:** For example, when the standard deviation is significantly greater at the high end versus the low end of a measuring interval.

imprecision – dispersion of independent results of measurements obtained under specified conditions; **NOTE:** It is expressed numerically as standard deviation or coefficient of variation.

intended use – use for which a product, process, or service is intended according to the specifications, instructions, and information provided by the manufacturer (ISO 14971).[13]

least squares regression – the method of statistically placing the location of the estimated line or curve among the data so that the sum of the squares of the distances of each data point from the line in the perpendicular direction from the x-axis (ie, parallel to the y-axis) is minimized; **NOTE:** It allows the direct algebraic computation of the coefficients and an estimate of their uncertainty.

matrix – all components of a material system, except the analyte (modified from ISO 15193).[14.]

matrix effect – influence of a property of the sample, independent of the presence of the analyte, on the measurement and thereby on the measured quantity value (ISO 15194)[13]; **NOTE:** The physicochemical effect(s) (eg, interference) of the matrix on the measurement procedure's ability to accurately measure an analyte.

measurand – quantity intended to be measured (JCGM 200:2012) [10]; **NOTE:** The term "measurand" and its definition encompass all quantities, while the commonly used term "analyte" refers to a tangible entity subject to measurement (ie, the measurand describes what is causing the result of the measurement, and the analyte describes the particular component of interest to the patient).

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). [10]

observed response – the measured physical or chemical parameter used to identify or quantify an analyte in comparison to an appropriate calibration system; **NOTE:** The observed response may be used by a system's internal processor and, therefore, the value is often not available to the testing personnel; examples include absorbance units, radioactive counts, and millivolt readings.

ordinary linear regression (OLR) – least squares linear regression that usually refers to nonweighted least squares regression.

processed sample – for the purposes ofEP14, a sample that is prepared to be used to mimic one obtained from a patient; **NOTE 1:** It is considered a processed sample if it has been modified in any way that causes it to be different from one obtained from a patient, eg, freezing, lyophilization, adding nonendogenous substances or stabilizers; **NOTE 2:** For EP14, these are the materials being evaluated for matrix effects.

proficiency testing/external quality assessment (PT/EQA) – a program in which multiple samples are periodically sent to members of a group of laboratories for analysis and/or identification, in which each laboratory's results are compared to an accepted reference value or to results from other laboratories in the group.

sample – one or more parts taken from a primary sample (ie, a discrete portion of a body fluid, breath, hair, or tissue taken for examination, study, or analysis of one or more quantities or properties assumed to apply for the whole) (ISO 15189)[15]; **EXAMPLE:** A volume of serum taken from a larger volume of serum (ISO 15189).[15]

specificity – the ability of a test or procedure to correctly identify or quantify an entity in the presence of interfering phenomena/influence quantities; **NOTE 1:** In quantitative testing, the ability of a measurement procedure to determine only the component it purports to measure or the extent to which the assay responds only to all subsets of a specified analyte and not to other substances present in the sample; **NOTE 2:** For qualitative or semiquantitative tests, the measurement procedure's ability to obtain negative results in concordance with negative results obtained by the reference measurement procedure.

trueness – closeness of agreement between the average value obtained from a large series of test results and an accepted reference value (ISO 5721-1).[16]

Type I error – occurs when a true null hypothesis is rejected (ie, one concludes that a false alternative hypothesis is true). The likelihood of committing a Type I error is specified by the alpha level a researcher employs in evaluating the experiment.[17]

1.4.3 Symbols

Below is a list of symbols used in the text and in the appendixes. Additional symbols used in the document are defined later in context.

α	true intercept of a method comparison regression
β	true slope of a method comparison regression
ˆ	symbol designating that the parameter factor shown below it is an estimate (eg, $\hat{\beta}$ is an estimate of regression slope as opposed to β which is the hypothetical model's true slope)
ε	random error of the parameter or factor shown in subscript below (eg, $\varepsilon_{\bar{Y}}$ is the random error of the Y replicate means)
γ	type I error rate, or the likelihood of falsely rejecting the null hypothesis
H	subscript designating patient sample(s)
$\hat{\lambda}$	ratio of the variances of random errors of the two measurement procedures (within-run or repeatability when data are collected in a single run).
n	number of patient samples tested
Pc	subscript designating processed sample(s)
Pc_pred	subscript designating predicted processed sample result from regression parameters
N_H	number of replicates for a patient sample's average test result
N_{Pc}	number of replicates for a processed sample's average test result
v	degrees of freedom of a regression estimate
$\bar{X}$	average of test results of a sample(s) from a measurement procedure plotted on the X axis of an X-Y graph.
$\bar{Y}$	average of test results of a sample from a measurement procedure plotted on the Y axis of an X-Y graph.

1.4.4 Abbreviations and Acronyms

CEN	Comité Européen de Normalisation (European Committee for Standardization)
EQA	external quality assessment
ISO	International Organization for Standardization
OLR	ordinary linear regression
PI	prediction interval
PT	proficiency testing
QC	quality control
SD	standard deviation

2 Commutability Determination Process

Because few, if any, measuring techniques are analytically specific, the observed relationship between any two measurement procedures will depend on the choice of the samples selected for comparison.[18,19] For clinical laboratory analysis, measurement procedures are designed to quantitate measurand in patient samples, and a representative set of these samples is used as the standard of this comparison.

Commutability is determined by comparison of the measured result for a processed sample to the "scatter" of results for a representative set of patient samples measured using two measurement procedures. The more heterogeneous the patient samples, in terms of any interfering or cross-reacting substances, the larger the scatter expected in the data.

The mean value for the processed sample(s) is compared with the scatter of the patient sample means about the regression line through patient sample results. This scatter represents the interval of differences

of measurement by the two measurement procedures due to two factors: imprecision and nonspecificity. The contribution of imprecision is reduced by replicate measurements in both procedures and comparing the mean values; therefore, in these analyses, interferences due to substances that are known or unknown (here called a "matrix effect") are easier to discern from random measurement error. The range of the scatter of these means is represented by the (PI), which includes the nonspecificity of the effects of the procedure(s) for all patient samples. It is then possible to assert with reasonable probability whether the processed sample can be used to represent the set of patient samples for the analyte being measured[20]; if the processed sample(s) result(s) is outside of the PI, noncommutability in these samples is considered likely.

Any conclusions from the study are limited to the specific components of the processed samples (eg, sources of analytes used to supplement the sample, types of stabilizers that might be present) and the measurement procedures (even reagent lot number) used.

2.1 Process Flow Chart

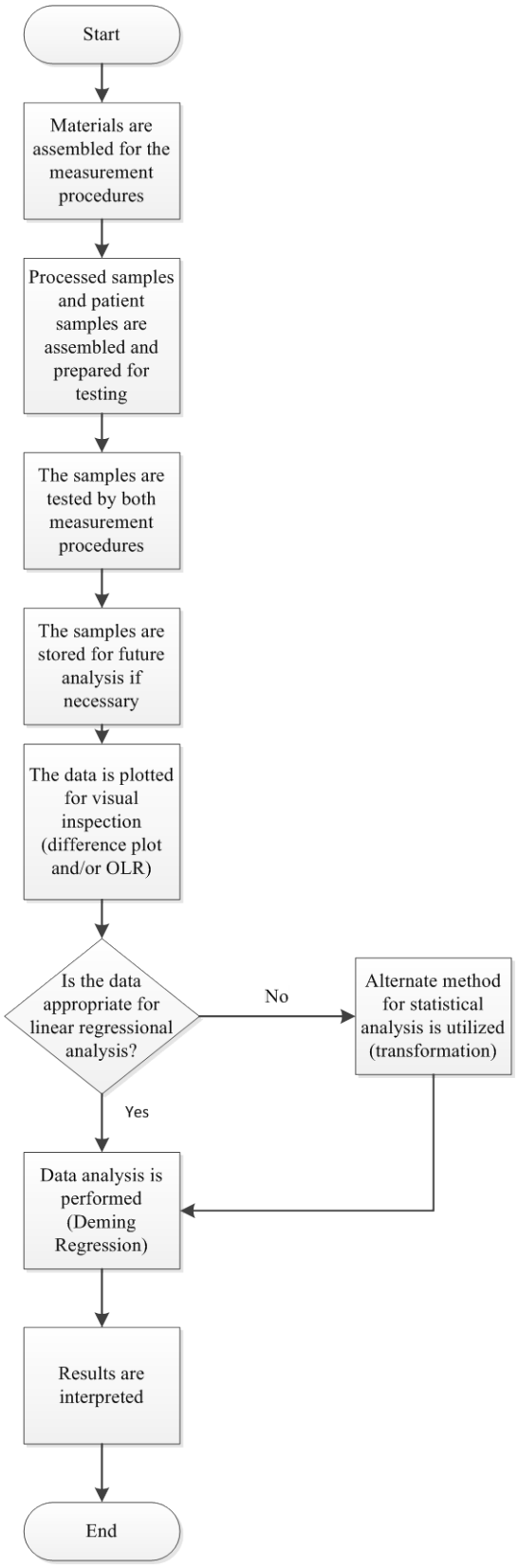


Figure 1. Process Flow Chart for Evaluation of Commutability for Processed Samples

2.2 Materials and Samples Assembly

2.2.1 Materials

The following materials are needed for this protocol:

- Reagents, calibrators, and instrument systems for which a material will be evaluated to be commutable. **NOTE:** The intent of this protocol is to use one lot of reagent per measurement procedure. However, commutability characteristics of a given processed sample may vary with different reagent lots.

  – It is ideal if one of the measurement procedures is likely to be minimally affected by sample matrix. When this is the case, a judgment can be made that a material is or is not suitable for use with a particular measurement procedure under investigation. Measurement procedures likely to be minimally affected by sample matrix are well-characterized reference measurement procedures that use effective sample cleanup to isolate the measurand of interest from other matrix components (eg, isotope dilution-liquid chromatography/tandem mass spectrometry for cholesterol), or well-characterized measurement procedures that use a sample preparation and chemical reaction that has been shown to be minimally affected by matrix components (eg, the hexokinase measurement procedure for glucose).

  In many cases, the "ideal" measurement procedure may not be available. The lack of such a measurement procedure in the comparison means that a result indicating noncommutability of the processed sample is equally likely to be due to processed sample interaction with measurement procedure A as with measurement procedure B, or even with both measurement procedures.

2.2.2 Samples

The following samples are needed for this protocol:

- Processed samples to be examined (eg, reference materials, PT/EQA samples, measuring interval sample sets, QC samples).

- At least 20 patient samples in the same form as specified by the measurement procedure manufacturer, eg, "fresh" if the test requires fresh samples, or "frozen" if the test uses frozen samples. The samples should have measurand concentrations or activities that are approximately evenly distributed over the range of results of the processed samples with concentrations at the medical decision level(s). Select patient samples that are typically used for analysis (eg, from both healthy and ill patients), and avoid those that are considered inappropriate for analysis because of the presence of known interferences or cross reacting substances. Frozen samples may be included if freezing does not affect the measurements of either measurement procedure.

  Samples spiked with the measurand should be avoided, if possible, because the use of such samples may result in an incorrect assessment of commutability. If it is impractical to obtain patient samples with results that cover the range of results of the processed samples without such spiked samples, then they should be identified in the scatter plot as spiked and inspected to determine if they follow the same linear pattern as unspiked samples.

  Increasing the sample size beyond 20 patient samples may be considered, it should be noted, however, that the benefit of increased sample size increases only by the square root of n as n gets larger. In simulations, it was shown that 20 patient samples were sufficient for detection of matrix

effects given average estimates of assay errors, although there were some moderate benefits from increasing the sample size to 40 (see CLSI document EP09)[6].

2.3 Measurement Procedure

2.3.1 Analysis

1. Using one of the measurement procedures, analyze as a single analytical batch the 20 or more patient samples with the processed samples randomly interspersed among the fresh patient samples. Analyze three or more replicates of each sample with the replicates in sequence in the batch. This same number of replicates (*N*) should be measured for each patient and processed sample (see note below). The result for each sample is the average of all replicates for that sample.

2. Using the other measurement procedure, analyze (as a single analytical run or batch) the same 20 or more patient samples, with the same processed samples randomly interspersed among patient samples. Analyze the patient samples and processed samples at the same time using each of the measurement procedures. Analyze three or more replicates of each sample with the replicates in sequence in the batch. In most cases, the same number of replicates (N) will be measured for each patient and processed sample (see note below). The result for each sample is the average of the three or more replicates for that sample.

   NOTE: Processed samples may be more homogenous than patient samples and therefore their repeatability may be better. If this is known and quantified, then the number of patient sample replicates may be increased, or the number of processed sample replicates decreased, to ensure that the variance is similar for the average result for both types of samples. By the same token, the measurement procedures may have different repeatability. The number of replicates within each measurement procedure can also be adjusted if these repeatability differences are known and quantified.

   If simultaneous analysis is not possible using both measurement procedures, information should be available to demonstrate that measurement procedure results are not changed by the storage conditions used for the patient samples and for the processed samples for whichever measurement procedure(s) requires such storage.

2.3.2 Postmeasurement sample storage

For future analysis, store under conditions validated to maintain stability of the sample aliquots of the patient samples and processed samples. If any questions arise during or after data analysis, the samples may be reanalyzed using another measurement procedure for which commutability evaluation is needed in relation to the measurement procedures already evaluated. Keep in mind that storage conditions, such as freezing, may introduce a matrix effect by altering binding proteins, enzyme conformation, etc.

2.4 Data Analysis

2.4.1 Data Visualization wWith Ordinary Regression

As often occurs in statistical analysis, the user is asked to judge the utility and appropriateness of the statistical test for each dataset. In these analyses, linearity, heteroscedasticity, and the imprecision of each measurement procedure could affect the interpretation of results. Incorrect assumptions increase the difficulty of detecting a matrix effect, and the PI from the patient sample set will be wider. The user should keep in mind the intended purposes of each study. Standard statistical textbooks can be referenced.

Plot the means of replicates of the patient samples with measurement procedure B results on the y-axis and measurement procedure A results on the x-axis (see Figure 2). At this stage, an OLR using the calculation for both intercept as well as slope of the regression line (ie, do not force the regression line through the origin) can be used to perform an initial evaluation.

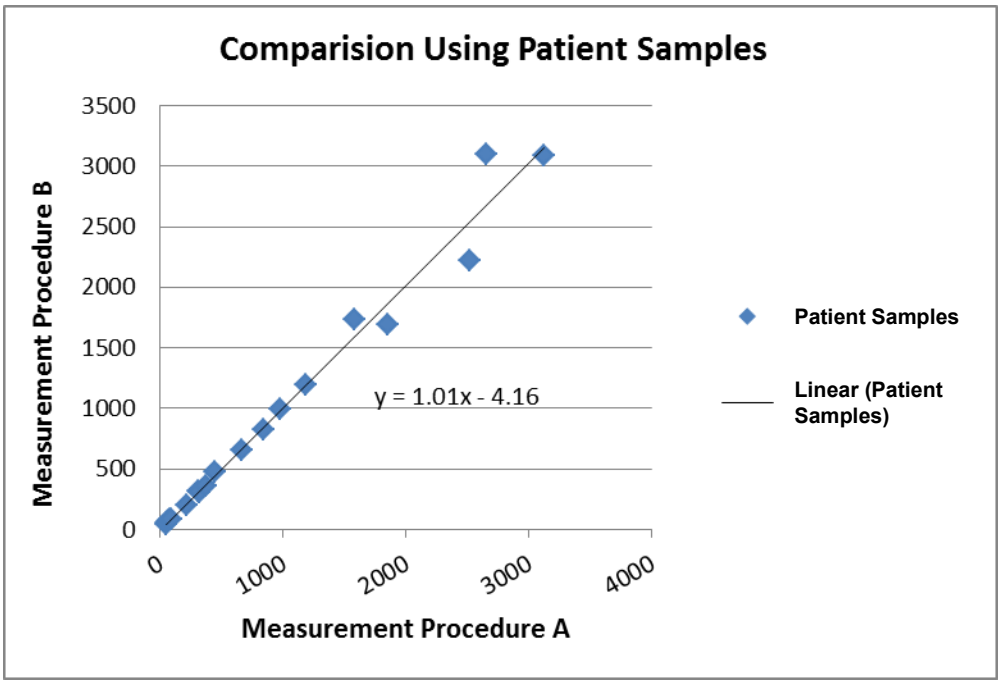


Figure 2. OLS Comparison of Patient Samples

Check the appropriateness of the data for linear regression analysis (see CLSI document EP09[6]). If the data are appropriate for linear regression but outliers are visually apparent, use the outlier detection process described in Appendix B. Alternative methods may be used as long as they are statistically valid and scientifically sound. **NOTE:** Even if potential outliers are found to be statistically significant, sound rationale for removal of outliers (eg, strong evidence of instrument or operator error) and replacement with additional data needs to be documented.

2.4.2 Data Visualization by Distribution of Means

1. Examine the distribution of the means of results from the patient samples obtained using measurement procedure B and measurement procedure A and verify the following prerequisites:

   – Examine the scatter of patient sample means between measurement procedures A and B using a difference plot (see Figure 3). This shows the difference between the measurement procedure's results (Y-axis) plotted versus their average (X-axis) for each patient sample. If the magnitude of the differences tends to increase with increasing measurand content, then proceed to Step 2. If the differences appear generaly constant, then proceed to Step 3.

2. If the variation in measurement procedure differences appears to increase in proportion to the measurand concentration, rather than being constant across the concentration range, perform a log10 transformation on the results of measurement procedures A and B, then average them. Using these transformed values, create another difference plot (see Figure 4) and assess the behavior of the differences. If the differences still tend to increase with the mean values, then other transformations may be tried on the original mean results.

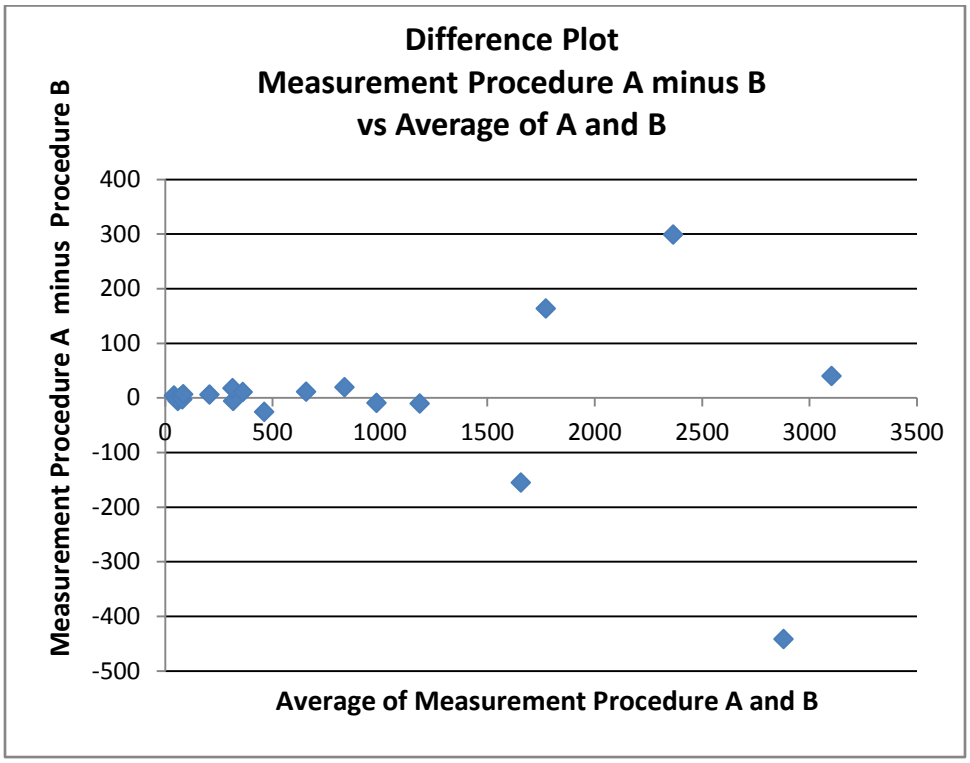


Figure 3. Difference Plot: Measurement Procedure A minus B vs Average of A and B

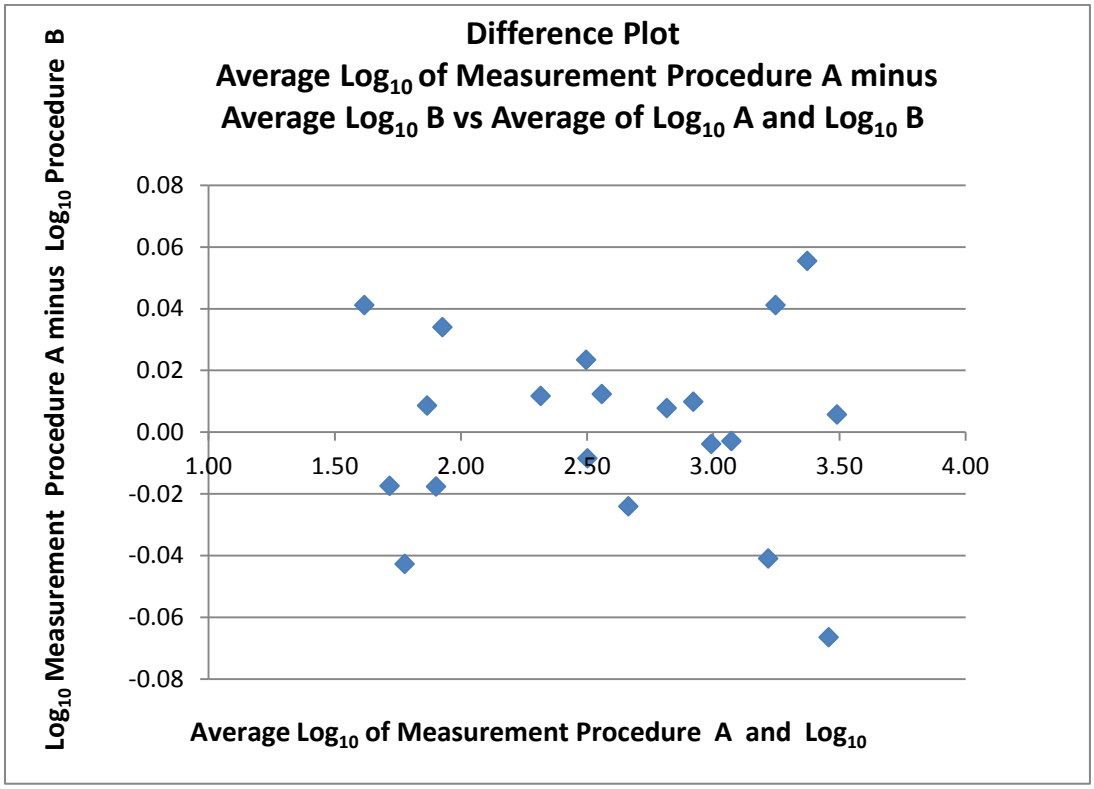


Figure 4. Difference Plot: Log_{10} of Measurement Procedure A – Log_{10} B vs Average of Log_{10} A and Log_{10} B

If the difference plot of the transformed means shows no discernable pattern of variation with concentration, proceed to Step 3.

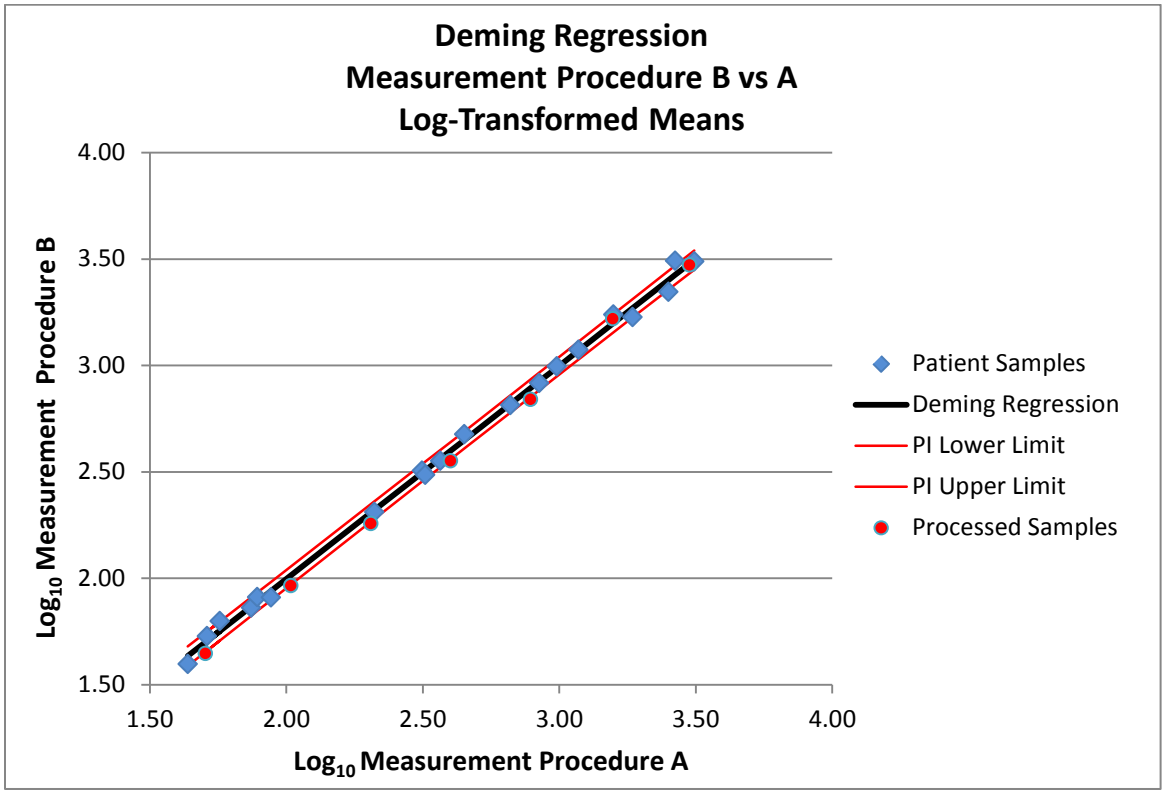
3. Perform Deming linear regression analysis using the patient sample means (or transformed means, as appropriate). Graph the means of measurement procedure B as the y-value and the means of measurement procedure A as the x-value. The patient sample means obtained from both procedures used in the Deming regression analysis will be calculated from either transformed or untransformed replicates based on the pattern of the scatter of results noted above. The processed samples will be treated the same as the patient samples and plotted on the same graph using different symbols.

2.4.3 Comparison of Processed Samples to the Patient Sample Deming Regression Line

If one assumes that each patient sample and candidate processed sample result measured by measurement procedures A and B is an average of the same number of *N* replicate measurements, and the variance is constant over the measuring intervals for each measurement procedure, then a 95% PI for the regression relationship between results for patient samples measured by these two procedures represents the limits within which a future result (based on *N* replicate measurements) will fall with a probability of 95%. Similarly, a commutable processed sample that behaves in the same manner as patient samples (ie, is commutable or does not have matrix effects), will have its measured value (based on same number of replicate measurements) within these limits with a probability of 95%.

The following is an overview of the process of Deming regression commutability evaluation, which is described in detail in Appendix A:

Calculate the Deming regression parameters and plot the 95% PIs based upon the patient samples. Then plot the average of each measurement procedures' result ($\overline{X}_{Pc}, \overline{Y}_{Pc}$) on the same graph for each of the processed samples. When the $\overline{X}_{Pc}, \overline{Y}_{Pc}$ result for that unique processed sample falls inside the PI limits, then that unique processed sample is considered to be commutable; otherwise, it is considered to be noncommutable. Figure 5 illustrates a transformed dataset with processed samples that are commutable.

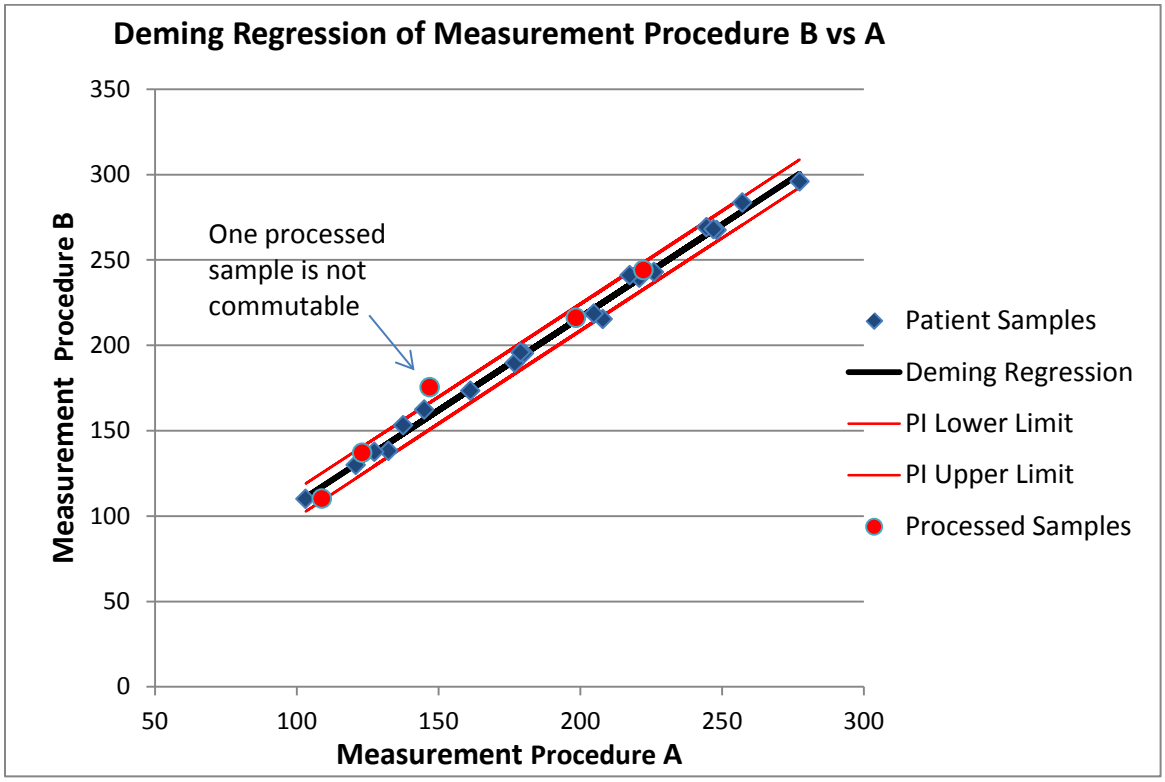


Abbreviation: PI, prediction interval.

Figure 5. Deming Regression of Log-Transformed Means

NOTE: Even when the processed samples (or some defined interval of them) are considered to be commutable, there still may be an apparent but statistically insignificant systematic bias (noncommutability) across the interval of the processed samples (see Appendix C, Example C1). The methodology and statistical analysis are not designed to provide estimates for this noted systematic bias. Any remedial actions based upon this finding would require further testing and analysis to better characterize this bias.

If the processed sample result falls outside the 95% PI for the patient samples, the processed sample would be considered noncommutable. This is illustrated in Figure 6.



Abbreviation: PI, prediction interval.

Figure 6. Deming Regression of Measurement Procedure B vs Measurement Procedure A

2.5 Documenting Results of the Commutability Evaluation

Although scatterplots including the Deming regression fit may be the preferred method for visualizing results of the commutability evaluation, data can also be reported numerically and tabulated for more precise demonstration of the degree of commutability, or lack thereof. This will serve to complement the graphic display, help to make decisions in borderline cases, and expound on the data in context.

The user is reminded that if large differences exist in specificity of the measurement procedure(s) used, a large PI will result, making this procedure less effective or ineffective. On the other hand, noncommutability that is statistically significant might not be clinically or quantitatively important.

3 Conclusion

EP14 was developed to assist in the education of clinical laboratorians, regulators, and diagnostic manufacturers about the commutability of processed materials, and how a processed sample's matrix can affect some measurand values and their interpretation (referred to as matrix effects).

This guideline should help all interested parties not only by evaluating a processed sample's commutability, but also by increasing awareness that there may be different levels of risk to the quality of patient care that are dependent on the intended use of a processed matrix.

4 Supplemental Information

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Appendix A. Description of Mathematical Model Used for Evaluating Commutability of Processed Samples Using Deming Regression

The method described here is similar to that described in CLSI document EP30[1] with some simplifications and improvements.

When a set of patient samples is measured by two different measurement procedures, it is expected that the relationship between the measured values will follow a linear relationship.[2] Under the preceding conditions, the relationships between the results for the two methods can be presented for the native clinical samples and the processed sample as

$$Y = \alpha_H + \beta_H X \quad (1a)$$
$$Y = \alpha_{Pc} + \beta_{Pc} X \quad (1b)$$

where:

α_{Pc}, α_H = intercepts,
β_{Pc}, β_H = slopes,

and the subscripts *H* and *Pc* indicate patient samples (human) and processed samples, respectively.

Note that the number of replicates in the equations that follow use the single annotation $N_{H.}$ This implies that the same number of replicates is used for both human (*H*) and processed samples (*Pc*). This also implies that the same number of samples is used for both measurement procedures. As described in the document text, if the repeatabilities of the measurement procedures or the sample types are different and this difference is known, then the user may choose to have different numbers of replicates for each situation. In such a case, the averages computed in Equations 4, 6 and 12 should use the number of replicates for each sample determination, rather than a common annotation $N_{H.}$

The equivalence of the mathematical relationships in Equations (1a) and (1b) would be established by showing that the respective model parameters are equal pairwise:

$$\alpha_{Pc} = \alpha_H \quad (2a)$$
$$\beta_{Pc} = \beta_H \quad (2b)$$

Equations (2a) and (2b) assume no measurement error. With measurement errors in both measurement procedures, Equation (1a) for the patient samples can be expressed as:

$$Y = \alpha_H + \beta_H(X + \varepsilon_X) + \varepsilon_Y \quad (3)$$

where $\varepsilon_X, \varepsilon_Y$ are random errors in the *X* and *Y* measurement procedures. Equation (3) parameters can be estimated with data using regular Deming regression under the following assumptions: the random errors $\varepsilon_X, \varepsilon_Y$ are independent (across the measurement procedures, samples, and replicates) and normally distributed with 0 means and have constant, measurand level-independent SDs, $\sigma(\varepsilon_X), \sigma(\varepsilon_Y)$. If these assumptions do not apply to the obtained data, transformations must be performed as described in Section 2.4 of this document.

The SDs, $\hat{\sigma}(\varepsilon_{X_i}), \hat{\sigma}(\varepsilon_{Y_i})$, of the replicate measurements are calculated for the i^{th} patient sample using the following equations:

Appendix A. (Continued)

$$\hat{\sigma}\left(\varepsilon_{X_i}\right)=\sqrt{\frac{1}{\left(N_H-1\right)}\sum_{j=1}^{N_H}\left(X_{ij}-\bar{X}_i\right)^2} \tag{4a}$$

$$\hat{\sigma}\left(\varepsilon_{Y_i}\right)=\sqrt{\frac{1}{\left(N_H-1\right)}\sum_{k=1}^{N_H}\left(Y_{ik}-\bar{Y}_i\right)^2} \tag{4b}$$

where:

N_H = number of replicates (the same for each patient sample), and
j = replicate for $\bar{X}_i$
k = replicate for $\bar{Y}_i$

When the SDs of both measurement procedures Y and X are approximately constant over the concentration interval examined, Equation (3) is fitted using regular Deming regression to the replicate means of the results of measurement. When the SDs of both measurement procedures Y and X are approximately proportional to the measurand level, Equation (3) is fitted using regular Deming regression to the replicate means of the logarithms of the results of measurement. In the calculations that follow, $\bar{X}_i, \bar{Y}_i$ are the replicate means when the SDs of the random measurement errors are approximately constant, and they are the means of the logarithms of replicate measurement results when the SDs are approximately proportional to the measurand level.

Equation (3) can be rewritten for the replicate means as:

$$\bar{Y}_i = \alpha_H + \beta_H(\bar{X}_i + \varepsilon_{\bar{X}_i}) + \varepsilon_{\bar{Y}_i} \tag{5}$$

where $\varepsilon_{\bar{X}}, \varepsilon_{\bar{Y}}$ are random errors of the replicate means.

The replicate means of the measurement results (or of their logarithms) obtained with the i^{th} patient sample (i = 1, 2, …, n) are calculated as:

$$\bar{X}_i=\frac{1}{N_H}\sum_{j=1}^{N_H}X_{ij} \tag{6a}$$

$$\bar{Y}_i=\frac{1}{N_H}\sum_{k=1}^{N_H}Y_{ik} \tag{6b}$$

Regular Deming regression provides unbiased minimum variance estimates of Equation (5) parameters $\hat{\alpha}_H, \hat{\beta}_H$ (from Miller RG Jr.,[2] with modified notation; equation for $\hat{\beta}_H$ assumes positive $\hat{\sigma}_{\overline{XY}}$, which is the case with clinical laboratory measurement procedures):

Appendix A. (Continued)

$$\hat{\beta}_H = \frac{\hat{\sigma}_{\bar{Y}}^2 - \hat{\lambda}\hat{\sigma}_{\bar{X}}^2 + \sqrt{(\hat{\sigma}_{\bar{Y}}^2 - \hat{\lambda}\hat{\sigma}_{\bar{X}}^2) + 4\hat{\lambda}\sigma_{\bar{X}\bar{Y}}^2}}{2\hat{\sigma}_{\bar{X}\bar{Y}}} \quad (7)$$

$$\hat{\alpha}_H = \bar{\bar{Y}} - \hat{\beta}_H\bar{\bar{X}} \quad (8)$$

$$\hat{\sigma}_{\bar{X}}^2 = \frac{1}{n}\sum_{i=1}^{n}(\bar{X}_i - \bar{\bar{X}})^2 \quad (9a)$$

$$\hat{\sigma}_{\bar{Y}}^2 = \frac{1}{n}\sum_{i=1}^{n}(\bar{Y}_i - \bar{\bar{Y}})^2 \quad (9b)$$

$$\hat{\sigma}_{\bar{X}\bar{Y}} = \frac{1}{n}\sum_{i=1}^{n}(\bar{X}_i - \bar{\bar{X}})(\bar{Y}_i - \bar{\bar{Y}}) \quad (9c)$$

$$\bar{\bar{X}} = \frac{1}{n}\sum_{i=1}^{n}\bar{X}_i \quad (10a)$$

$$\bar{\bar{Y}} = \frac{1}{n}\sum_{i=1}^{n}\bar{Y}_i \quad (10b)$$

$$\hat{\lambda} = \hat{\sigma}^2(\varepsilon_Y)/\hat{\sigma}^2(\varepsilon_X) \quad (11)$$

where:

n	=	number of patient samples used for fitting Equation (5),
$\bar{\bar{X}}, \bar{\bar{Y}}$	=	means across measurement results obtained with *X* and *Y* measurement procedures with patient samples (grand means),
$\hat{\sigma}_{\bar{X}}^2, \hat{\sigma}_{\bar{Y}}^2, \hat{\sigma}_{\bar{X}\bar{Y}}$	=	mean squares and mean cross-product of the deviations of the replicate means of results of measurements obtained with the *X* and *Y* measurement procedures from the respective grand means, and
$\hat{\lambda}$	=	ratio of the variances of random errors of the two measurement procedures (ratio of within-run or repeatabilities when data are collected in a single run).

The constant, measurand level-independent, random error variance estimates $\hat{\sigma}^2(\varepsilon_X), \hat{\sigma}^2(\varepsilon_Y)$ are calculated as follows (the equations are modified for a constant number of replicates for both measurement procedures and each sample)[3]:

$$\hat{\sigma}^2(\varepsilon_X) = \frac{1}{n(N_H - 1)}\sum_{i=1}^{n}\sum_{j=1}^{N_H}(X_{ij} - \bar{X}_i)^2 \quad (12a)$$

$$\hat{\sigma}^2(\varepsilon_Y) = \frac{1}{n(N_H - 1)}\sum_{i=1}^{n}\sum_{k=1}^{N_H}(Y_{ik} - \bar{Y}_i)^2 \quad (12b)$$

Appendix A. (Continued)

Each of the above variances has $n(N_H - 1)$ degrees of freedom. The variances of the means of N_H replicate results of measurements calculated with Equation (6) are N_H times smaller than the variances of the individual results given in Equation (12).

Assuming the processed samples are commutable with the patient samples for measurement procedures *Y* and *X,* the result of measurement on a processed sample with *Y* measurement procedure, Y_{Pc}, is a linear function of the result of measurement on the processed sample with *X* measurement procedure, X_{Pc}:

$$Y_{Pc} = \alpha_H + \beta_H X_{Pc} \tag{13}$$

The last equation can be re-expressed for predicted value, $\overline{Y}_{\mathbf{Pc}\_pred}$, by substituting Equation (8) into Equation (13) for $\hat{\alpha}_H$ and including the random errors:

$$\overline{Y}_{\mathrm{Pc}\_pred} = \overline{\overline{Y}} + \hat{\beta}_H \left(\left(\overline{X}_{Pc} - \overline{\overline{X}} \right) + \left(\varepsilon_{\overline{X}} + \varepsilon_{\overline{\overline{X}}} \right) \right) + \left(\varepsilon_{\overline{Y}} + \varepsilon_{\overline{\overline{Y}}} \right) \tag{14}$$

The random error of the slope, $\hat{\beta}_H$, estimated with the patient samples, is independent of the errors of measurements on the processed sample, and the latter are mutually independent across the two measurement procedures. Therefore, from Equation (14), the standard deviation of the prediction error is:

$$\sigma(\bar{Y}_{\mathrm{Pc}\_pred}) \approx \sqrt{\left(\overline{X}_{Pc} - \overline{\overline{X}} \right)^2 \hat{\sigma}^2_{\beta H} + \hat{\beta}^2_H \left(\hat{\sigma}^2 \left(\varepsilon_{\overline{X}} \right) + \hat{\sigma}^2 \left(\varepsilon_{\overline{\overline{X}}} \right) \right) + \left(\hat{\sigma}^2 \left(\varepsilon_{\overline{Y}} \right) + \hat{\sigma}^2 \left(\varepsilon_{\overline{\overline{Y}}} \right) \right)} \tag{15a}$$

Taking into account that in the above equation the sums of variances can be expressed as:

$$\hat{\sigma}^2 \left(\varepsilon_{\overline{X}} \right) + \hat{\sigma}^2 \left(\varepsilon_{\overline{\overline{X}}} \right) = \hat{\sigma}^2 \left(\varepsilon_{\overline{X}} \right) \left(1 + 1/n \right) = \hat{\sigma}^2 \left(\varepsilon_X \right) \left(1 + 1/n \right) / N_{Pc} \tag{15b}$$

$$\hat{\sigma}^2 \left(\varepsilon_{\overline{Y}} \right) + \hat{\sigma}^2 \left(\varepsilon_{\overline{\overline{Y}}} \right) = \hat{\sigma}^2 \left(\varepsilon_{\overline{Y}} \right) \left(1 + 1/n \right) = \hat{\sigma}^2 \left(\varepsilon_Y \right) \left(1 + 1/n \right) / N_{Pc} \tag{15c}$$

the standard deviation of the prediction error is:

$$\sigma(\bar{Y}_{\mathrm{Pc}\_pred}) \approx \sqrt{\left(\overline{X}_{Pc} - \overline{\overline{X}} \right)^2 \hat{\sigma}^2_{\beta H} + \left(\hat{\beta}^2_H \hat{\sigma}^2 \left(\varepsilon_X \right) + \hat{\sigma}^2 \left(\varepsilon_Y \right) \right) \left(1 + 1/n \right) / N_{Pc}} \tag{16}$$

The variance of random error of the slope estimate is calculated as[4]:

$$\hat{\sigma}^2_{\beta H} = \frac{\hat{\beta}^2_H}{n \hat{\sigma}^2_{\overline{X}\overline{Y}}} (\hat{\sigma}^2_{\overline{X}} \hat{\sigma}^2_{\overline{Y}} - \hat{\sigma}^2_{\overline{X}\overline{Y}}) \tag{17}$$

The values of the mean squares and mean cross-product in Equation (17) are calculated using Equations (9a) to (9c) above.

The lower, *L*, and upper, *U*, limits of the $(1-\gamma)100\%$ PI for $\overline{Y}_{Pc}$ are calculated as

$$\left[L, U \right] = Y_{\mathbf{Pc}\_pred} \mp t(1 - \gamma/2, n(N_H - 1)) \cdot \hat{\sigma}(\overline{Y}_{\mathbf{Pc}\_pred}) \tag{18}$$

Appendix A. (Continued)

γ = probability of type 1 error of false rejection of the hypothesis of commutability, typically 0.05, corresponding to 95% PI.

$t(1-\gamma/2, n(N_H-1))$ = $(1-\gamma/2)100$ - percentile of the two-tailed t – distribution with $n(N_H-1)$ degrees of freedom.

Commutability of the reference materials is established by drawing the straight line described by the equation:

$$Y = \hat{\alpha}_H + \hat{\beta}_H X, \tag{19}$$

calculating and drawing the 95% prediction bounds in the same graph, and, finally, plotting the $\overline{Y}_{Pc}, \overline{X}_{Pc}$ points in the same graph. When the $\overline{Y}_{Pc}, \overline{X}_{Pc}$ fall(s) inside the prediction bounds, the processed sample is considered to be commutable; otherwise, it is considered not to be commutable.

To verify the described above method of calculating the PIs around Deming regression line, Monte Carlo simulation was performed. Deviations of the proportion of results within prediction limits from the expected proportion were between -0.013 and +0.007 in 4 million simulated prediction intervals for 16 combinations of confidence level (95%; 90%), slope (0.96; 1.04), intercept (0.11; -0.12), standard deviation of random errors (0.6; 0.8) and numbers of replicates of clinical and processed samples (3; 10) for 250,000 of simulated PIs per combination.

NOTE: If the processed samples under evaluation are related, (eg, admixtures of the same high and low PT/EQA samples, or manufactured at the same time using the same base matrix), as is the case in many instances, then to reduce Type I error (incorrect rejection of the true null hypothesis, or, in this protocol, the chance of wrongly concluding there is a difference between the processed samples' and the patient samples' responses), the value for γ (Type I error rate) can be divided by the number of processed samples being evaluated. However, it is arguably more important to have low probability of Type 2 error of falsely accepting the hypothesis of commutability, which is complimentary to the power (probability) to detect noncommutability of processed sample. In other words, the power to detect noncommutability of processed sample is the probability that $\overline{Y}_{Pc}, \overline{X}_{Pc}$ result for noncommutable processed sample is outside the PI. It depends on the width of the PI and on the criteria of noncommutability expressed in terms of critical distance of $\overline{Y}_{Pc}, \overline{X}_{Pc}$ from the Deming regression line fitted with the data collected with clinical samples. The required power can be obtained by tightening the PI through increase of n, N_H and N_{Pc}. Details of calculations to obtain the required power to detect noncommutability is out of scope of this document, and the user may need to consult experts on establishing criteria of noncommutability and calculations of the power to detect noncommutability.

References for Appendix A

1 CLSI. *Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Approved Guideline.* CLSI document EP30-A. Wayne, PA: CLSI; 2008.

2 CLSI. *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.* CLSI document EP06-A. Wayne, PA: CLSI; 2003.

3 Draper NR, Smith H. Applied Regression Analysis, 3rd ed. New York, NY: John Wiley & Sons; 1998: 291-298.

4 Miller RG Jr. *Beyond ANOVA: Basics of Applied Statistics.* New York, NY: John Wiley & Sons; 1986:220-230.

5 Kendall MG, Stuart A. *The Advanced Theory of Statistics*. Vol. 2. 4th ed. New York, NY: Oxford University Press; 1979:406-407.

Appendix B. Outlier Evaluation for a Measurement Procedure Comparison Using Deming Regression

All equations referenced in this appendix are those from Appendix A.

1. Collect results of measurements with $N_H \geq 3$ replicates (the same number of replicates for each clinical sample, to simplify the calculations) on a measurand of interest with a pair of measurement procedures of interest, *Y* and *X,* for $n \geq 20$ patient samples, with concentrations spanning the interval of concentrations of the processed samples, in a single run per measurement procedure.

2. Calculate replicate means, $\bar{Y}_i, \bar{X}_i$, ($i = 1, 2, \ldots n$) using Equation (6) in Appendix A.

3. Plot SDs, $\hat{\sigma}(\varepsilon_{X_i}), \hat{\sigma}(\varepsilon_{Y_i})$, of the replicate results of measurements calculated with Equations (4a) and (4b) in Appendix A vs replicate means $\bar{X}_i$ and $\bar{Y}_i$, respectively.

   Given the transformation performed in Section 2.4 of this document, the SDs for both *Y* and *X* measurement procedures should appear to be independent of the measurand level. If so, proceed with the next step. If not, then additional iterations of Box-Cox transformations[1] can be used until the SDs of the logarithms of the replicates are practically independent of the measurand level and constant over the range of the patient samples.

4. Calculate variances of random errors of measurement with measurement procedures *Y* and *X* calculated with Equations (12a) and (12b) in Appendix A vs replicate means and the SDs as the square roots of the former: $\sigma(\varepsilon_X)=\sqrt{\sigma^2(\varepsilon_X)}, \sigma(\varepsilon_Y) = \sqrt{\sigma^2(\varepsilon_Y)}$. Check for replicate outliers in the procedure *Y* and *X* results with the Studentized range test:

   $X_{i,max} - X_{i,min} > q\sigma(\varepsilon_X)$ and/or $Y_{i,max} - Y_{i,min} > q\sigma(\varepsilon_Y)$.

   The 99th percentile of q is given in a table of the referenced publication[2] for various numbers of degrees of freedom of the SD and the number of replicates. The constant SD that is independent of the measurand level in Equation (12) has $n(N_H - 1)$ degrees of freedom. The probability for the set of results of measurement (N_H replicate results obtained with the pair of measurement procedures) to satisfy the above inequalities and belong to the normal population of the results is approximately $2 \cdot 0.01 = 0.02$; therefore, such a set of results for the i^{th} patient sample is considered to be an outlier that is removed from further analysis. As a general rule, no more than 5% of the data should be flagged and removed as an outlier(s), and the number of patient samples available for further analysis after possible removal of the outliers should be at least 20, as mentioned in Step 1. Critical values of q for several sample sizes of the patient samples and of the numbers of replicate measurements derived from the table in the referenced publication[2] are given in Table B1 (some of the values were interpolated).

Appendix B. (Continued)

Table B1. Critical *q* Values

Sample Size *n*	Number of Replicate Measurements N_H	Number of Degrees of Freedom *v*	99th Percentile of Studentized Range *q*
20	3	40	4.37
	4	60	4.59
	5	80	4.78
	6	100	4.91
30	3	60	4.28
	4	90	4.55
	5	120	4.71
	6	150	4.85
40	3	80	4.25
	4	120	4.50
	5	160	4.68
	6	200	4.81

For other sample sizes, *n* between 20 and 40, *q* can be interpolated using the values in the table.

References for Appendix B

[1] Box GEP, Cox DR. An analysis of transformations. *J Roy Stat B Met.* 1964;B26:211-252.

[2] Beyer HB, ed. *CRC Handbook of Tables for Probability and Statistics.* 2nd ed. Boca Raton, FL: CRC Press; 1968:362.

Appendix C. Examples of Completed Analyses

Example C1. Data Requiring No Transformation

Data are collected from two measurement procedures for cholesterol using 20 patient samples and five processed samples. In these data, the measurand is cholesterol and the unit is mg/dL. The replicate results are shown in Table C1. **NOTE**: The number of significant figures shown in the table and calculations are higher than standard practice to assist the user when checking Deming regression calculations.

Table C1. Example C1 Dataset

		Measurement Procedure A mg/dL X-axis			Measurement Procedure B mg/dL Y-axis		
Patient Sample	**Run Order**	***N* 1**	***N* 2**	***N* 3**	***N* 1**	***N* 2**	***N* 3**
1	21	206.27	213.13	204.53	217.43	208.78	219.86
2	10	143.71	146.45	144.76	161.57	161.95	163.32
3	22	118.59	117.81	126.21	127.43	133.14	129.01
4	8	224.56	231.18	222.17	246.47	236.57	245.42
5	9	249.09	248.05	247.22	266.61	274.72	261.04
6	25	206.03	205.60	202.75	217.59	215.63	222.02
7	5	220.74	224.57	217.09	236.31	241.65	240.33
8	1	175.12	173.99	181.63	182.33	191.41	195.36
9	3	242.66	245.04	245.72	269.62	272.50	265.39
10	14	162.58	158.43	162.55	177.67	169.33	173.15
11	18	131.18	137.38	128.50	137.68	131.66	144.67
12	3	242.84	247.71	250.34	264.58	270.42	268.85
13	19	133.99	140.23	138.34	155.64	153.43	150.03
14	15	226.87	209.17	216.33	238.32	241.54	242.92
15	24	259.22	257.44	254.87	285.09	283.05	282.53
16	20	180.03	178.13	182.35	188.97	200.60	196.30
17	17	99.39	106.08	103.99	110.16	108.02	111.61
18	12	276.38	279.19	276.34	284.93	298.46	304.16
19	6	126.17	132.06	123.88	135.89	138.10	138.66
20	4	181.95	173.08	181.81	192.45	201.37	193.65
Processed Sample							
a	2	107.17	106.39	113.02	117.60	107.32	105.53
b	13	122.86	124.04	122.47	131.54	140.26	139.05
c	11	150.00	143.63	147.22	182.85	170.44	172.81
d	16	198.39	200.01	196.92	215.74	221.86	210.35
d	7	221.84	221.94	223.17	250.75	241.86	239.59

Abbreviation: *N,* replicate.

Appendix C. (Continued)

To evaluate whether the difference of the means ($\overline{Y}_i - \overline{X}_i$) of the patient results for each measurement procedure is dependent on the concentration, the differences can be plotted against the average concentration of each procedure. If measurement procedure A is a reference measurement procedure, the differences can be plotted against the mean of the reference measurement procedure. An OLR and difference plot of the patient samples shows that the variability of the differences (scatter) appears to be independent of concentration. See Figures C1 and C2.

NOTE: A standard scatter plot of the data has less resolution than a difference plot because the range of each axis is at least as wide as the range of each measurement procedure's results, whereas the Y-axis range of the difference plot is only as wide as the biggest difference between measurement procedure results.

Figure C1 shows the Example C1 sample plot for cholesterol.

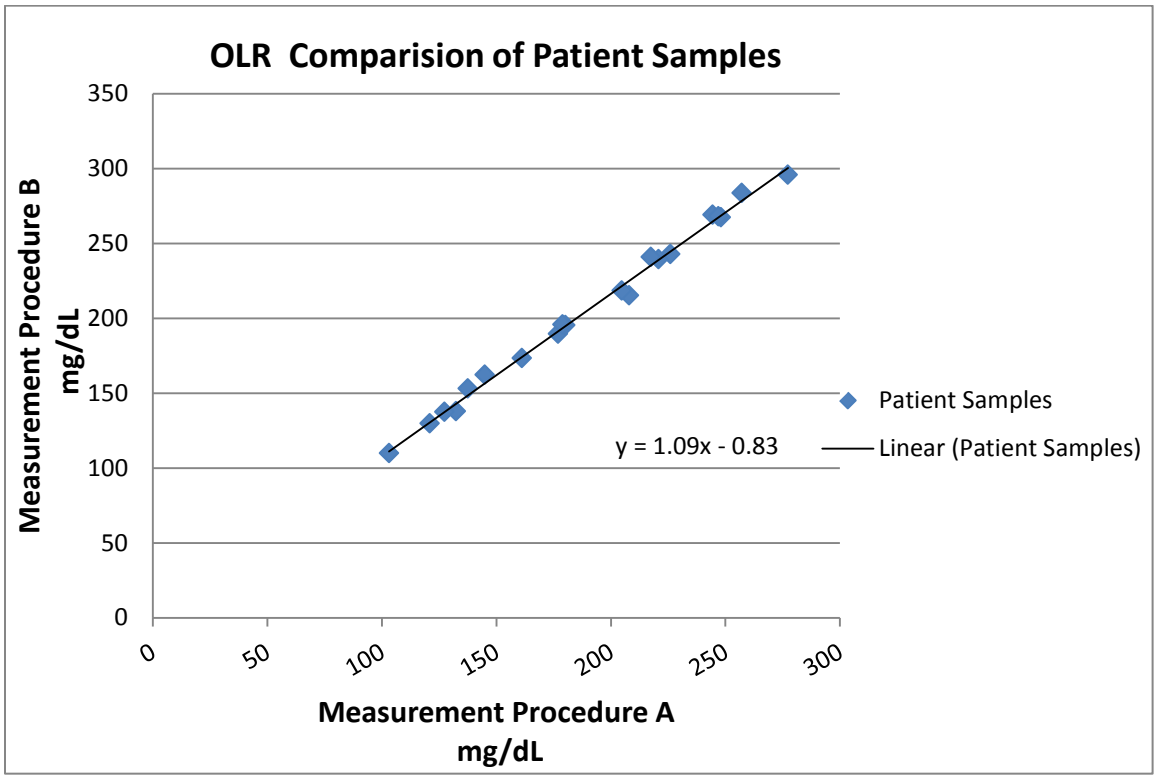


Figure C1. OLR Comparison of Patient Samples for Example 1

Appendix C. (Continued)

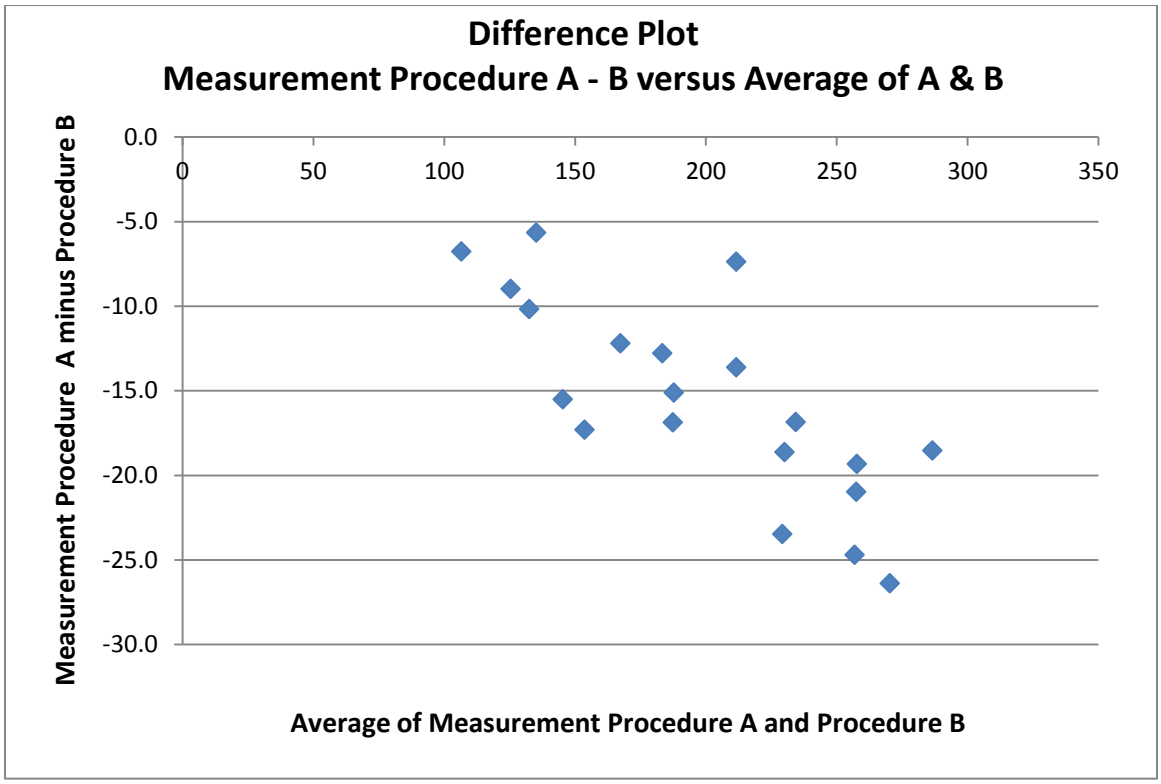


Figure C2. Difference Plot: Measurement Procedure A minus B vs A and B Average for Example C1

Then, using the calculations described in Appendix A, evaluate the means of the replicates for each of the measurement procedures' results using a Deming regression. The results of the calculations and the Appendix A equations used are shown below. Please note that since Appendix A equations describe Deming regression theory, the calculations that follow are in a different sequence and some intermediate steps are omitted.

Equations (7) and (8) define the parameters of the Deming regression line.

$$\hat{\beta}_H = \frac{\hat{\sigma}_{\bar{Y}}^2 - \hat{\lambda}\hat{\sigma}_{\bar{X}}^2 + \sqrt{(\hat{\sigma}_{\bar{Y}}^2 - \hat{\lambda}\hat{\sigma}_{\bar{X}}^2) + 4\hat{\lambda}\sigma_{\bar{X}\bar{Y}}^2}}{2\hat{\sigma}_{\bar{X}\bar{Y}}}$$

$$\hat{\alpha}_H = \bar{\bar{Y}} - \hat{\beta}_H\bar{\bar{X}}$$

The means of each sample's X and Y and then grand means are calculated first using Equations 10a and 10b.

$$\bar{\bar{X}} = \frac{1}{n}\sum_{i=1}^{n}\bar{X}_i = 191$$

Appendix C. (Continued)

$$\bar{\bar{Y}} = \frac{1}{n}\sum_{i=1}^{n}\bar{Y}_i = 206$$

The sum of squares for X and Y and their cross product is calculated next using Equations (9a, 9b, and 9c).

$$\hat{\sigma}_{\bar{X}}^2 = \frac{1}{n}\sum_{i=1}^{n}(\bar{X}_i - \bar{\bar{X}})^2 = 2541$$

$$\hat{\sigma}_{\bar{Y}}^2 = \frac{1}{n}\sum_{i=1}^{n}(\bar{Y}_i - \bar{\bar{Y}})^2 = 3011$$

$$\hat{\sigma}_{\bar{X}\bar{Y}} = \frac{1}{n}\sum_{i=1}^{n}(\bar{X}_i - \bar{\bar{X}})(\bar{Y}_i - \bar{\bar{Y}}) = 2760$$

To obtain λ we need to calculate the random error variances per Equations (12a and 12b).

$$\hat{\sigma}^2(\varepsilon_X) = \frac{1}{n(N_H - 1)}\sum_{i=1}^{n}\sum_{j=1}^{N_H}(X_{ij} - \bar{X}_i)^2 = 15.06$$

$$\hat{\sigma}^2(\varepsilon_Y) = \frac{1}{n(N_H - 1)}\sum_{i=1}^{n}\sum_{k=1}^{N_H}(Y_{ik} - \bar{Y}_i)^2 = 22.08$$

So that Equation (11):

$$\hat{\lambda} = \hat{\sigma}^2(\varepsilon_Y)/\hat{\sigma}^2(\varepsilon_X) = 1.466$$

And Equation (7):

$$\hat{\beta}_H = \frac{\hat{\sigma}_{\bar{Y}}^2 - \hat{\lambda}\hat{\sigma}_{\bar{X}}^2 + \sqrt{(\hat{\sigma}_{\bar{Y}}^2 - \hat{\lambda}\hat{\sigma}_{\bar{X}}^2)^2 + 4\hat{\lambda}\hat{\sigma}_{\bar{X}\bar{Y}}^2}}{2\hat{\sigma}_{\bar{X}\bar{Y}}} = 1.088$$

Equation (8):

$$\hat{\alpha}_H = \bar{\bar{Y}} - \hat{\beta}_H\bar{\bar{X}} = -1.282$$

Equation (16) is used to calculate the PI limits.

Appendix C. (Continued)

Equation (16):

$$\sigma(\bar{Y}_{\mathrm{Pc\_}pred}) \approx \sqrt{\left(\bar{X}_{Pc} - \bar{\bar{X}}\right)^2 \hat{\sigma}^2_{\beta H} + \left(\hat{\beta}^2_H \hat{\sigma}^2\left(\varepsilon_X\right) + \hat{\sigma}^2\left(\varepsilon_Y\right)\right)\left(1 + 1/n\right)/N_{Pc}}$$

And remembering that the random error variances (Equations 12a and 12b):

$$\hat{\sigma}^2(\varepsilon_X) = \frac{1}{n(N_H - 1)} \sum_{i=1}^{n} \sum_{j=1}^{N_H} (X_{ij} - \bar{X}_i)^2 = 15.06$$

$$\hat{\sigma}^2(\varepsilon_Y) = \frac{1}{n(N_H - 1)} \sum_{i=1}^{n} \sum_{k=1}^{N_H} (Y_{ik} - \bar{Y}_i)^2 = 22.08$$

And the variance of the random error of the slope estimate per Equation (17):

$$\hat{\sigma}^2_{\beta H} = \frac{\hat{\beta}_H^{\,2}}{n\hat{\sigma}^2_{\bar{X}\bar{Y}}} (\hat{\sigma}^2_{\bar{X}} \hat{\sigma}^2_{\bar{Y}} - \hat{\sigma}^2_{\bar{X}\bar{Y}}) = 2.9 \cdot 10^{-4}$$

If $\bar{X}_{Pc} = 145.0$ then $\bar{Y}_{Pc\_pred} = 156.5$ then Equation (16)

$$\sigma(\bar{Y}_{\mathrm{Pc\_}pred}) \approx \sqrt{\left(\bar{X}_{Pc} - \bar{\bar{X}}\right)^2 \hat{\sigma}^2_{\beta H} + \left(\hat{\beta}^2_H \hat{\sigma}^2\left(\varepsilon_X\right) + \hat{\sigma}^2\left(\varepsilon_Y\right)\right)\left(1 + 1/n\right)/N_{Pc}} = 3.82$$

Equation (18):

$$\left[L, U\right] = Y_{\mathbf{Pc\_}pred} \mp t(1 - \gamma/2, n(N_H - 1)) \cdot \hat{\sigma}(\bar{Y}_{\mathbf{Pc\_}pred})$$

The two-tailed t value for $p = 0.05$ and $n(N_H\text{-}1) = 40$ degrees of freedom are used.

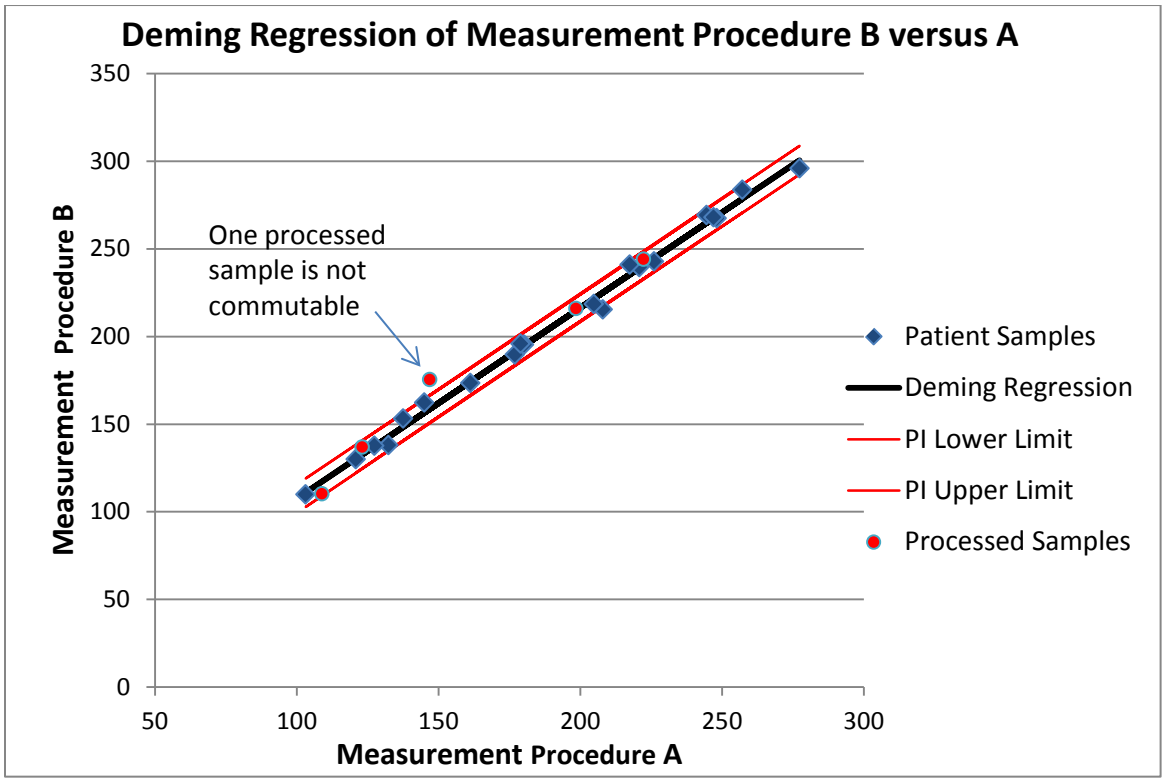
$t = 2.021$

The PI limits at $\bar{Y}_{Pc\_pred} = 156.5$ is:

$\bar{Y}_{Pc\_pred} \pm t(1 - \frac{\gamma}{2}, n(N_H - 1) * \hat{\sigma}(\bar{Y}_{Pc\_pred}) =$ 148.8 to 164.2.

The regression of the Example C1 means of the patient samples with the processed sample points plotted on the same graph are shown in Figure C3. One of the processed samples is outside PI limits.

Appendix C. (Continued)



Abbreviation: PI, prediction interval.

Figure C3. Deming Regression of Measurement Procedure B vs Measurement Procedure A for Example C1

Conclusion: Processed sample "c" in Example C1, Table C1 exhibits a matrix effect that is different from the patient samples.

Example C2. Data Requiring Transformation

Data are collected from two measurement procedures for myoglobin using 20 patient samples and seven processed samples. In these data, the measurand is myoglobin and the unit is ng/mL. Example C2 replicate results are shown in Table C2. **NOTE:** The number of significant figures shown in the table and calculations are higher than standard practice to assist the user when checking Deming regression calculations.

Appendix C. (Continued)

Table C2. Example C2 Dataset

		Measurement Procedure A ng/mL X-axis			Measurement Procedure B ng/mL Y-axis		
Patient Sample	**Run Order**	***N* 1**	***N* 2**	***N* 3**	***N* 1**	***N* 2**	***N* 3**
1	6	81.22	77.01	76.44	80.74	82.22	81.34
2	16	1646.21	1603.92	1488.53	1800.98	1723.45	1680.66
3	2	54.16	55.23	62.00	66.01	62.84	60.04
4	21	1819.54	1829.46	1916.59	1751.11	1802.45	1521.11
5	26	40.03	46.25	44.55	41.23	39.32	38.30
6	15	2615.25	2490.13	2440.12	2083.66	2394.44	2172.02
7	20	220.34	210.36	200.00	204.97	209.83	198.78
8	13	461.21	450.23	435.11	500.25	471.42	452.21
9	18	77.30	74.37	71.20	71.15	77.10	70.33
10	4	700.23	653.91	633.12	701.12	643.87	608.41
11	22	380.70	364.58	355.62	365.12	356.31	348.40
12	9	2723.29	2734.05	2519.15	3331.11	3004.24	2966.66
13	12	868.44	854.53	810.62	800.14	852.06	824.17
14	8	54.67	45.03	54.73	55.21	54.05	50.93
15	7	90.82	88.03	84.72	83.70	81.20	78.83
16	23	3201.66	3156.39	3011.66	2929.75	3120.04	3200.70
17	1	351.20	320.40	298.72	321.00	301.21	295.77
18	14	1001.23	975.24	961.22	1050.10	943.41	972.82
19	11	1300.21	1120.29	1120.33	1352.00	1162.39	1059.08
20	5	325.31	316.92	300.13	331.20	312.49	317.16
Processed Sample							
a	27	789.34	769.43	792.23	655.22	725.51	695.44
b	3	407.02	387.99	402.00	344.50	355.10	370.05
c	25	1554.02	1572.04	1580.26	1750.12	1588.00	1625.55
d	24	104.09	98.36	109.23	85.02	92.77	99.55
e	10	3002.35	2978.68	3010.30	3105.22	2844.11	2951.00
f	19	210.36	203.05	199.27	170.29	182.37	190.11
g	17	50.34	49.29	52.04	40.45	42.31	50.25

Abbreviation: *N,* replicate.

In Figure C4, the differences were plotted against the average of both measurement procedures.

Appendix C. (Continued)

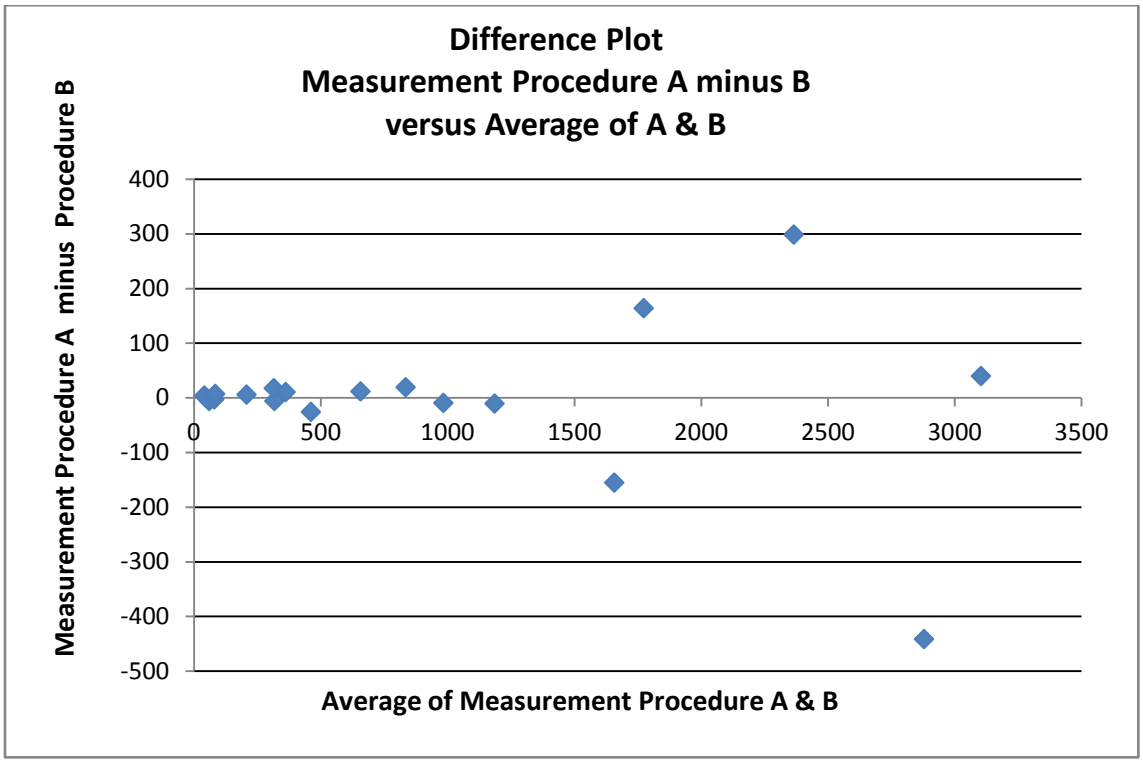


Figure C4. Difference Plot: Measurement Procedure A minus B versus A and B Average for Example C2

Because the magnitudes of the differences appear to increase in proportion at concentrations above 1500 ng/mL, the means of the $\log_{10}$ and the differences of the means of the $\log_{10}$ results are calculated in Table C3 and then plotted in Figure C5. This difference plot shows no pattern of the magnitude of the differences with concentration.

Appendix C. (Continued)

Table C3. Log10 Means and Log10 Differences of Example C2 Dataset

Patient Sample	$\text{Log}_{10}(\overline{X})$	$\text{Log}_{10}(\overline{Y})$	Mean	Difference
1	1.893	1.911	1.902	-0.018
2	3.199	3.239	3.219	-0.040
3	1.757	1.799	1.778	-0.042
4	3.268	3.228	3.248	0.040
5	1.640	1.598	1.619	0.042
6	3.401	3.346	3.374	0.055
7	2.323	2.311	2.317	0.012
8	2.652	2.676	2.664	-0.024
9	1.871	1.862	1.867	0.009
10	2.821	2.814	2.818	0.007
11	2.565	2.552	2.559	0.013
12	3.425	3.491	3.458	-0.066
13	2.927	2.917	2.922	0.010
14	1.712	1.728	1.720	-0.016
15	1.944	1.910	1.927	0.034
16	3.495	3.489	3.492	0.006
17	2.510	2.486	2.498	0.024
18	2.991	2.995	2.993	-0.004
19	3.072	3.076	3.074	-0.004
20	2.497	2.506	2.502	-0.009
Processed Sample				
a	2.894	2.840	2.867	0.054
b	2.601	2.552	2.577	0.049
c	3.196	3.219	3.208	-0.023
d	2.017	1.966	1.992	0.051
e	3.477	3.472	3.475	0.005
f	2.310	2.257	2.284	0.053
g	1.704	1.647	1.676	0.057

Appendix C. (Continued)

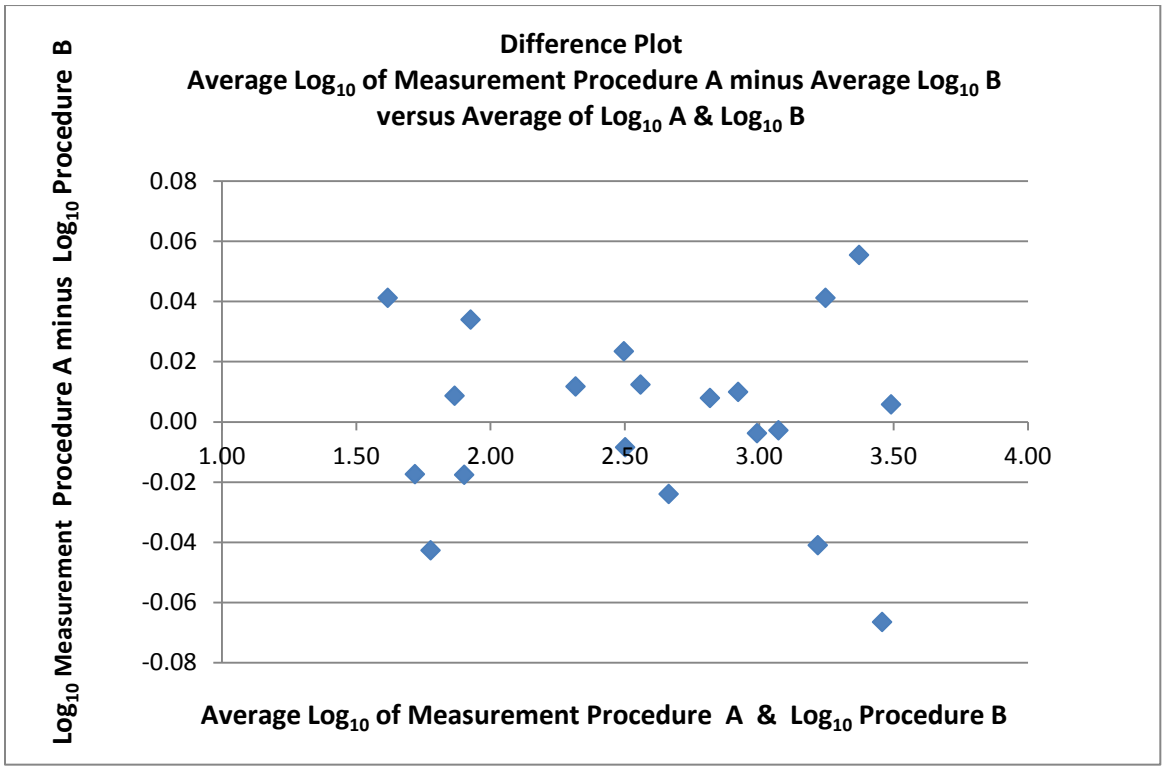


Figure C5. Difference Plot: Average Log_{10} of Measurement Procedure A minus Average Log_{10} Procedure B versus Average of Log_{10} A and Log_{10} B for Example C2

Then, with the calculations described in Appendix A, the log_{10}–transformed means of the replicates for each procedure are evaluated using a Deming regression. The results of the calculations and the Appendix A equations used are shown below.

Equations (7) and (8) define the parameters of the Deming regression line.

$$\hat{\beta}_H = \frac{\hat{\sigma}_{\bar{Y}}^2 - \hat{\lambda}\hat{\sigma}_{\bar{X}}^2 + \sqrt{(\hat{\sigma}_{\bar{Y}}^2 - \hat{\lambda}\hat{\sigma}_{\bar{X}}^2) + 4\hat{\lambda}\sigma_{\bar{X}\bar{Y}}^2}}{2\hat{\sigma}_{\bar{X}\bar{Y}}}$$

$$\hat{\alpha}_H = \bar{\bar{Y}} - \hat{\beta}_H\bar{\bar{X}}$$

Equation (9a, 9b, and 9c):

$$\hat{\sigma}_{\bar{X}}^2 = \frac{1}{n}\sum_{i=1}^{n}(\bar{X}_i - \bar{\bar{X}})^2 = 0.372$$

$$\hat{\sigma}_{\bar{Y}}^2 = \frac{1}{n}\sum_{i=1}^{n}(\bar{Y}_i - \bar{\bar{Y}})^2 = 0.374$$

Appendix C. (Continued)

$$\hat{\sigma}_{\bar{X}\bar{Y}} = \frac{1}{n}\sum_{i=1}^{n}(\bar{X}_i - \bar{\bar{X}})(\bar{Y}_i - \bar{\bar{Y}}) = 0.373$$

To obtain λ we need calculate the random error variances per Equations (12a and 12b)

$$\hat{\sigma}^2(\varepsilon_X) = \frac{1}{n(N_H - 1)}\sum_{i=1}^{n}\sum_{j=1}^{N_H}(X_{ij} - \bar{X}_i)^2 = 5.66x10^{-4}$$

$$\hat{\sigma}^2(\varepsilon_Y) = \frac{1}{n(N_H - 1)}\sum_{i=1}^{n}\sum_{k=1}^{N_H}(Y_{ik} - \bar{Y}_i)^2 = 5.71x10^{-4}$$

So that Equation (11):

$$\hat{\lambda} = \hat{\sigma}^2(\varepsilon_Y)/\hat{\sigma}^2(\varepsilon_X) = 1.009$$

Equation (7):

$$\hat{\beta}_H = \frac{\hat{\sigma}^2_{\bar{Y}} - \hat{\lambda}\hat{\sigma}^2_{\bar{X}} + \sqrt{(\hat{\sigma}^2_{\bar{Y}} - \hat{\lambda}\hat{\sigma}^2_{\bar{X}})^2 + 4\hat{\lambda}\sigma^2_{\bar{X}\bar{Y}}}}{2\hat{\sigma}_{\bar{X}\bar{Y}}} = 1.0026$$

Equation (8):

$$\hat{\alpha}_H = \bar{\bar{Y}} - \hat{\beta}_H\bar{\bar{X}} = -0.0081$$

Equation (16) is used to calculate the PI limits.

$$\sigma(\bar{Y}_{\mathrm{Pc\_}pred}) \approx \sqrt{\left(\bar{X}_{Pc} - \bar{\bar{X}}\right)^2 \hat{\sigma}^2_{\beta H} + \left(\hat{\beta}^2_H\hat{\sigma}^2\left(\varepsilon_X\right) + \hat{\sigma}^2\left(\varepsilon_Y\right)\right)\left(1 + 1/n\right)/N_{Pc}}$$

and remembering that the random error variances (Equations 12a and 12b)

$$\hat{\sigma}^2(\varepsilon_X) = \frac{1}{n(N_H - 1)}\sum_{i=1}^{n}\sum_{j=1}^{N_H}(X_{ij} - \bar{X}_i)^2 = 5.66x10^{-4}$$

$$\hat{\sigma}^2(\varepsilon_Y) = \frac{1}{n(N_H - 1)}\sum_{i=1}^{n}\sum_{k=1}^{N_H}(Y_{ik} - \bar{Y}_i)^2 = 5.71x10^{-4}$$

and the variance of the random error of the slope estimate per Equation (17).

Appendix C. (Continued)

$$\hat{\sigma}^2_{\beta H} = \frac{\hat{\beta}_H^{\,2}}{n\hat{\sigma}^2_{\bar{X}\bar{Y}}}(\hat{\sigma}^2_{\bar{X}}\hat{\sigma}^2_{\bar{Y}} - \hat{\sigma}^2_{\bar{X}\bar{Y}}) = 1.203 \cdot 10^{-4}$$

If $\bar{X}_{Pc} = 1.64$ then $\bar{Y}_{Pc\_pred} = 1.635$ then equation (16)

$$\sigma(\bar{Y}_{\mathrm{Pc}\_pred}) \approx \sqrt{\left(\bar{X}_{Pc} - \bar{\bar{X}}\right)^2 \hat{\sigma}^2_{\beta H} + \left(\hat{\beta}^2_H \hat{\sigma}^2\left(\varepsilon_X\right) + \hat{\sigma}^2\left(\varepsilon_Y\right)\right)\left(1 + 1/n\right)/N_{Pc}} = 0.0226$$

Equation (18):

$$\left[L, U\right] = Y_{\mathbf{Pc}\_pred} \mp t(1-\gamma/2, n(N_H - 1)) \cdot \hat{\sigma}(\bar{Y}_{\mathbf{Pc}\_pred})$$

The two-tailed t value for $p = 0.05$ and $n(N_H\text{-}1)$ degrees of freedom is used.

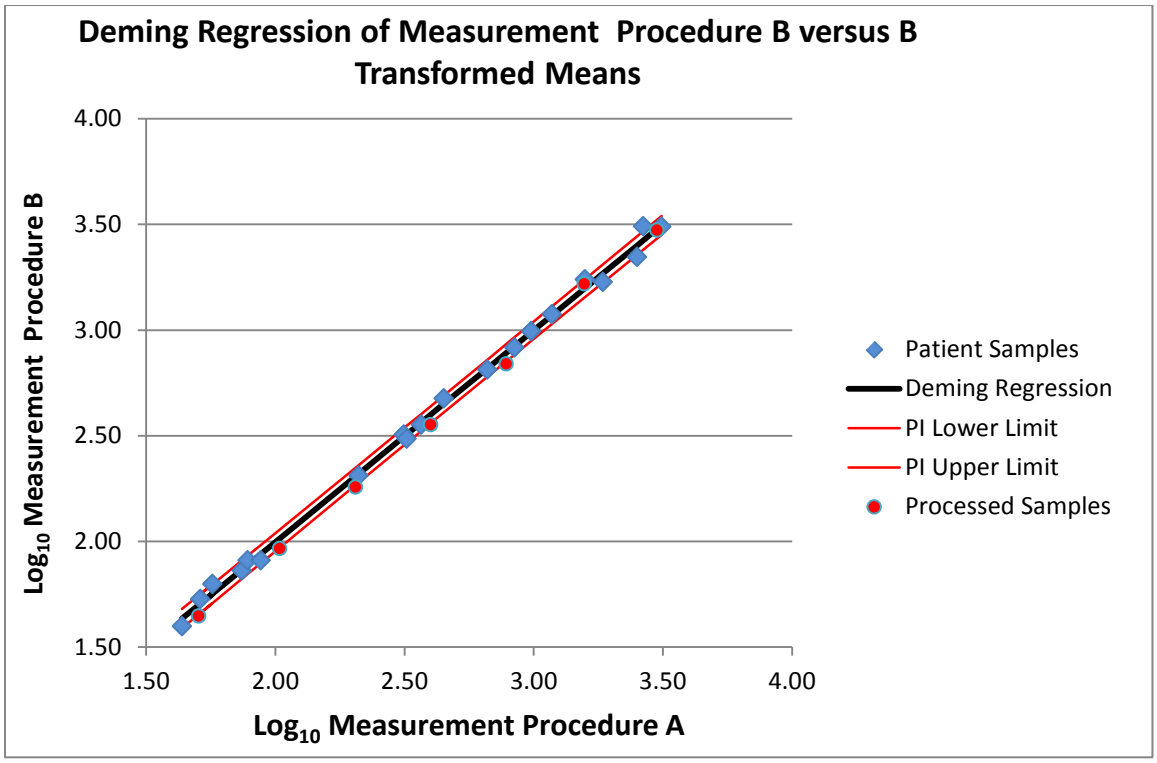
$t = 2.021$

The PI limits at $\bar{Y}_{Pc\_pred} = 1.635$ is:

$\bar{Y}_{Pc\_pred} \pm t_{1-\left(\frac{\gamma}{2}\right), n(N_H-1)} \hat{\sigma}(\bar{Y}_{Pc\_pred}) = 1.589$ to 1.681

The regression of the transformed means of the patient samples with the processed sample points plotted on the same graph are shown in Figure C6. All processed samples are within the PI limits demonstrating that they are commutable. Figure C7 shows that if the untransformed means are plotted using Deming regression, the error about the regression line changes in proportion to the concentration, which is undesirable.

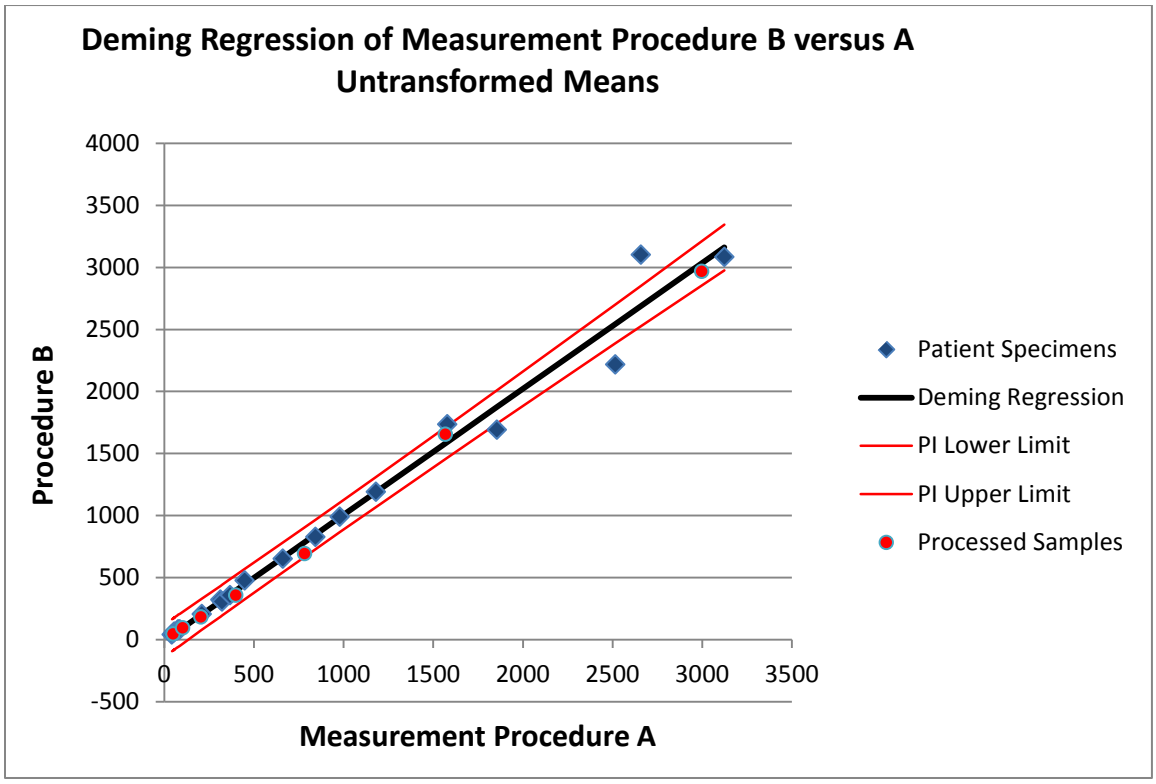
Appendix C. (Continued)



Abbreviation: PI, prediction interval.

Figure C6. Deming Regression of Log-transformed Means for Example C2

Appendix C. (Continued)



Abbreviation: PI, prediction interval.

Figure C7. Deming Regression of Measurement Procedure B vs A: Untransformed Means for Example C2

In this example, plotting the untransformed means of the patient samples and the processed samples shows the increased scatter of the results with increased concentration. Such a relationship does not meet the assumptions of a standard Deming regression.

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system (QMS) 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 QMS 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

EP14-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
		M29				X C59 EP06 EP09 EP15 EP26 EP30 EP32					

Path of Workflow

A path of workflow is the description of the necessary processes to deliver the particular product or service that the organization or entity provides. A laboratory path of workflow consists of the sequential processes: preexamination, examination, and postexamination and their respective sequential subprocesses. All laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

EP14-A3 addresses the clinical laboratory path of workflow step indicated by an "X." For a description of the other document listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Preexamination				Examination			Postexamination	
Examination ordering	Sample collection	Sample transport	Sample receipt/processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
					C59	X C59	C59	C59

Related CLSI Reference Materials*

C59-A **Apolipoprotein Immunoassays: Development and Recommended Performance Characteristics; Approved Guideline (1997).** This document provides guidance for the characterization and preparation of immunogens, antibodies, samples, and methods, as well as for immunochemical testing of apolipoproteins.

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.

EP15-A2 **User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (2006).** This document describes the demonstration of method precision and trueness for clinical laboratory quantitative methods utilizing a protocol designed to be completed within five working days or less.

EP26-A **User Evaluation of Between-Reagent Lot Variation; Approved Guideline (2013).** This document provides guidance for laboratories on the evaluation of a new reagent lot, including a protocol using patient samples to detect significant changes from the current lot.

EP30-A **Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Approved Guideline (2010).** This document provides information to help material manufacturers in the production and characterization of commutable reference materials, as well as to assist assay manufacturers and laboratorians in the appropriate use of these materials for calibration and trueness assessment of *in vitro* diagnostic medical devices.

EP32-R **Metrological Traceability and Its Implementation; A Report (2006).** This document provides guidance to manufacturers for establishing and reporting metrological traceability.

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.

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

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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)
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)
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)
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)
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)
The Good Samaritan Hospital (PA)
The Hospital for Sick Children (Canada)
The Korean Society for Laboratory Medicine
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)
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)
Dr. William Fales (MO)
Pilar Fernandez-Calle (Spain)
Leah Ferrier (MT)
Ms. Sue Forrest (Australia)
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