CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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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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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 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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