CLINICAL AND LABORATORY STANDARDS INSTITUTE®

1st Edition

EP35

Assessment of Equivalence or Suitability of Specimen Types for Medical Laboratory Measurement Procedures

This guideline provides recommendations for assessing clinically equivalent performance for additional similar-matrix specimen types and suitable performance for dissimilar-matrix specimen types, such that the laboratory does not necessarily need to repeat the full measurement procedure validation for each specimen type. The recommendations in this guideline apply to both quantitative measurement procedures and qualitative examinations.

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

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Assessment of Equivalence or Suitability of Specimen Types for Medical Laboratory Measurement Procedures

Nils B. Person, PhD, FAACC
Karafa SW Badjie, MS, MLS(ASCP)SBB, RT(CSMLS)
Abdel-Baset Halim, PharmD, PhD, DABCC
Kenneth Hoekstra, PhD, HCLD, FAACC
Marina V. Kondratovich, PhD
Qing H. Meng, PhD, MD, DABCC, FAACC
Victoria Petrides, MS
Richard Pfeltz, PhD

Abstract

Clinical and Laboratory Standards Institute guideline EP35—*Assessment of Equivalence or Suitability of Specimen Types for Medical Laboratory Measurement Procedures* provides information for assessing clinically equivalent performance for additional similar-matrix specimen types and suitable performance for dissimilar-matrix specimen types. During development, medical laboratory measurement procedures are typically validated for the most common specimen type. However, it can be clinically useful to test the measurand in multiple specimen types, including different fluids (eg, serum, plasma, whole blood, urine, cerebrospinal fluid, saliva), anticoagulants, and collection devices. By following the recommendations in this guideline, developers of laboratory measurement procedures do not necessarily need to repeat the full measurement procedure validation for each specimen type. EP35 applies to both quantitative measurement procedures and qualitative examinations. This guideline is useful to developers of commercial and laboratory-developed tests and medical laboratory personnel.

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Contents

Foreword

For measurement procedures whose performance characteristics have previously been validated with a primary specimen type, this guideline provides recommendations for assessing clinically equivalent performance for other similar-matrix specimen types and suitable performance for dissimilar-matrix specimen types. These assessments provide verification options that do not repeat full measurement procedure validation for the additional specimen types, which include different fluids (eg, serum, plasma, whole blood, urine, cerebrospinal fluid, saliva), anticoagulants (eg, EDTA, citrate, oxalate), and collection devices (eg, gel barrier, plain tube). To date, there is no general guidance on requirements or protocols for demonstrating multiple specimen type equivalence or suitability for use on measurement procedure performance. Multiple sources provide guidance (eg, anticoagulant testing in CLSI document EP07,[1] discussion of alternate body fluids in CLSI document C49,[2] specimen collection tube evaluation in CLSI document GP34[3]), but no CLSI documents provide the information as a cohesive whole. EP35 provides guidance on verifying clinically equivalent or suitable performance for additional specimen types without necessarily having to repeat the full measurement procedure validation for each specimen type. EP35 applies to both quantitative measurement procedures and qualitative examinations and is useful to developers of commercial and laboratory-developed tests and medical laboratory personnel.

Because measurement procedure performance characteristics can change when specimen types have substantially different matrix characteristics, evaluation of performance often needs to be based on suitability of the observed performance to the clinical requirements for the specific specimen type matrix rather than strict numerical equivalence. Therefore, access to the necessary clinical information is key to establishing equivalent or suitable performance for multiple specimen types, including the expected interval of measurand concentrations, inherent biological variability, medical decision levels, and any other relevant information for each specimen type. These characteristics can vary considerably between specimen types for the same measurand (eg, creatinine in serum vs urine). Once the necessary clinical information is available, the desirable measurement procedure performance attributes can be characterized for each specimen type based on risk assessment. After the performance requirements are established for each specimen type, the protocols described in this guideline can be used to document clinically equivalent or suitable performance.

NOTE: The content of this guideline is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

KEY WORDS

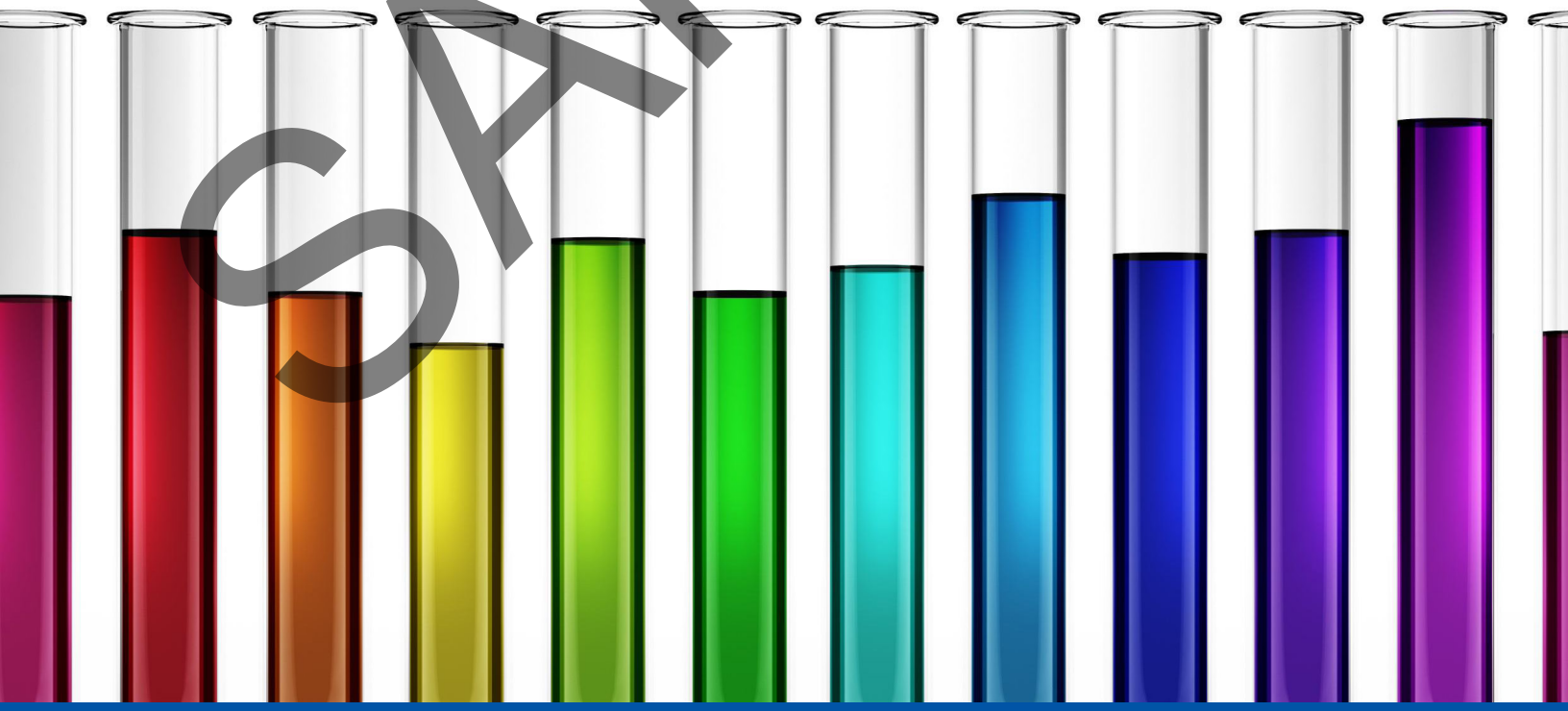
Candidate specimen type
Clinical equivalence
Clinical suitability
Equivalence
Primary specimen type
Specimen type
Suitable

Chapter 1

Introduction

This chapter includes:

- Guideline's scope and applicable exclusions
- Background information pertinent to the guideline's content
- Standard precautions information
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions
- Terms and definitions used in the guideline
- Abbreviations and acronyms used in the guideline



Assessment of Equivalence or Suitability of Specimen Types for Medical Laboratory Measurement Procedures

1 Introduction

1.1 Scope

This guideline provides a protocol for assessing equivalence or suitability for use of a different specimen type compared with the established primary specimen type for a medical laboratory measurement procedure or qualitative examination. This guideline provides a general framework for studies that establish equivalence among similar-matrix specimen types and clinical suitability among dissimilar-matrix specimen types. It also includes instructions for laboratory verification of alternate specimen types for commercial measurement procedures. This guideline applies to both quantitative measurement procedures and qualitative examinations. The intended users of this guideline are manufacturers, developers of medical laboratory measurement procedures, and laboratorians verifying alternate specimen types.

EP35 is intended to be used for specimen types for which the desired measurand has a known clinical indication and for which adequate clinical information is available to establish risk-based clinical performance goals. Establishing clinically based performance goals is beyond this guideline's scope.

EP35 focuses on the effect of specimen type on the analytical measurement procedure. There may also be preexamination factors between specimen types that can affect results. These differences may require additional studies to characterize their effect on the results. Such preexamination factors are outside of the scope of EP35.

1.2 Background

Medical laboratory measurement procedure performance characteristics are generally established and validated for use for the most commonly used specimen type for the measurand, which is designated as the primary specimen type. However, there is often a clinical need to measure the same measurand in a different specimen type (eg, urine rather than serum). Changing the specimen type can alter both the measurement procedure performance and the performance characteristics desirable for clinical use, so it is important to document that the measurement procedure performance characteristics are clinically acceptable with the candidate specimen type.

For specimen types with a similar matrix (eg, serum and plasma), the measurement procedure's performance can be tested for equivalence among specimen types. When the matrixes are dissimilar (eg, serum and urine), it might not be possible to establish equivalence (eg, because of different measuring intervals), but the new specimen type can still be shown to be clinically acceptable or suitable for use.

To assess specimen type equivalence or suitability, a definition of what constitutes equivalent or suitable performance is needed. Typically, equivalence is defined as the condition of being equal in value, worth, function, etc. In the context of establishing specimen types' equivalence or suitability for a measurement procedure, there are two primary scenarios.

3 Evaluation Plan Development

The evaluation plan goal is to establish equivalence or suitability of measurement procedure attributes between multiple specimen types and to determine how to proceed when the goal is not met.

3.1 Risk Assessment

With a new candidate specimen type, the risk of change in various measurement procedure attributes should be assessed (eg, linearity, precision, accuracy, specimen stability, clinically expected values). For each performance attribute identified as possibly changing, acceptable performance criteria need to be established based on clinical information.

The necessary clinical information for each specimen type includes:

- ☑ Expected range of concentrations
- ☑ Inherent biological variability
- ☑ Clinical importance (or lack thereof) of very low concentrations
- ☑ Any medical decision levels

With this information, risk evaluation can be used to determine the clinically acceptable performance criteria for each specimen type. For example, when the specimen types to be assessed are serum and urine, systematic differences in recovery or linearity can lead to increased clinical risk, so the criteria for systematic difference need to be as stringent as for comparison of two serum methods. Conversely, although there can be a significantly greater background biological variation for the measurand in urine compared with serum, the risk of greater imprecision in the urine measurement can be low. Therefore, the suitability criteria might not need to be as stringent as for comparison of two different serum methods. Understanding the associated clinical risks helps determine the management strategy, should there be lack of equivalence between specimen types.

3.2 Evaluation Plan Content

For each measurement procedure attribute, the evaluation plan should include:

- ☑ Study protocol to evaluate equivalence or suitability
- ☑ Acceptance criteria for equivalence or suitability

Recommended protocols for evaluating suitability for commonly assessed attributes are described in Chapter 4.

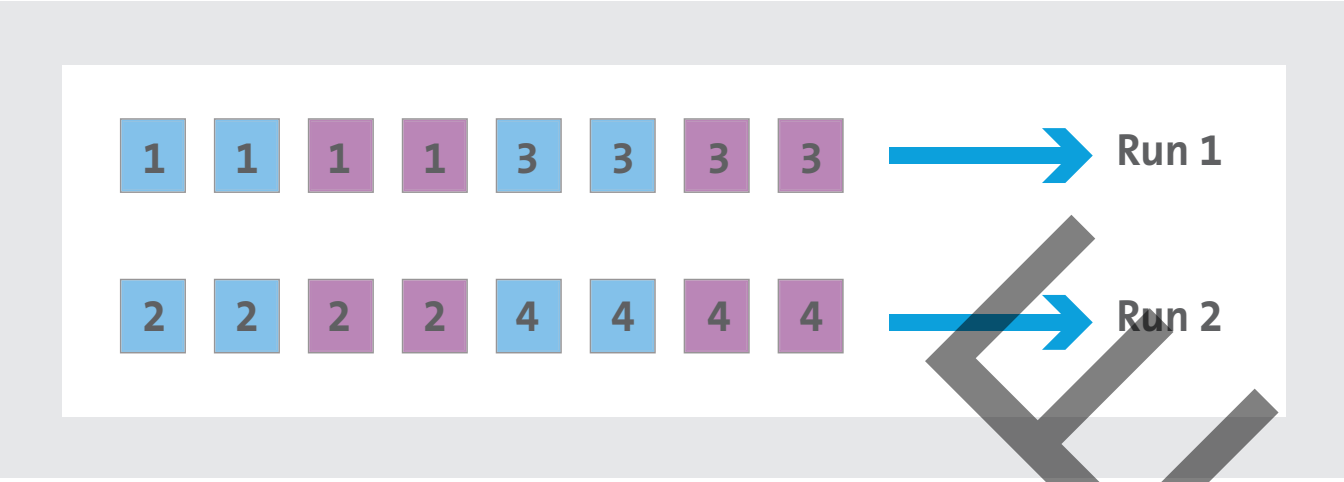


Figure 6. Study Design A. Blue boxes = primary specimen type; purple boxes = candidate specimen type.

- **Study design B:** The replicates are split across runs; eg, only a single replicate is tested for each specimen in each run (see Figure 7). In this study design, replicate results from the same specimens are obtained from different runs. The precision of both specimen types is compared with respect to repeatability and between-run components of variation. Apparent differences between specimen types can be due to differences between runs, but this study design minimizes these potential differences.

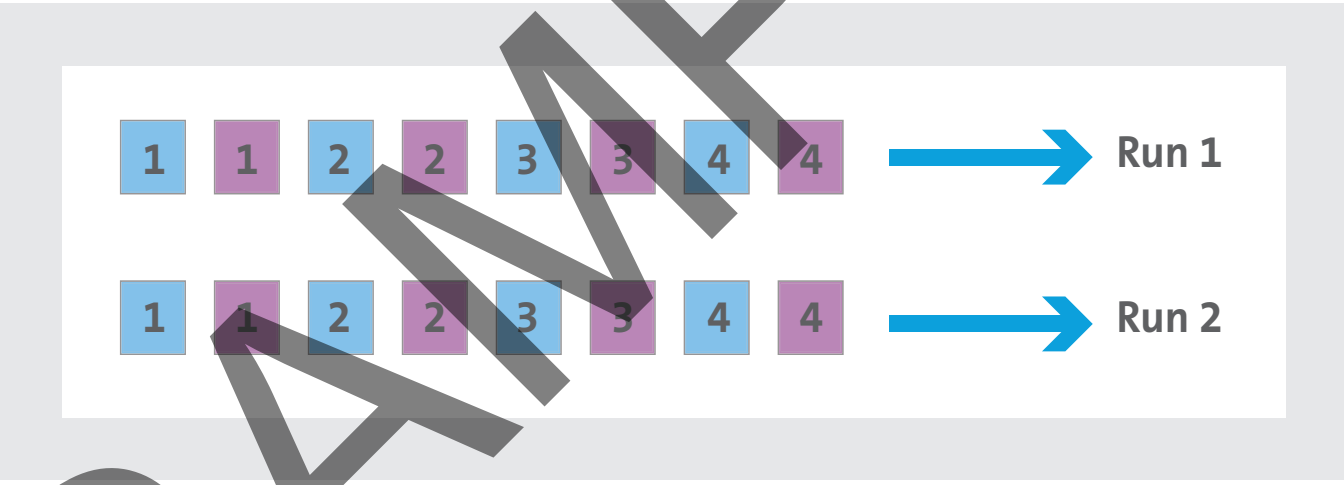


Figure 7. Study Design B. Blue boxes = primary specimen type; purple boxes = candidate specimen type.

Related CLSI Reference Materials*

C49 **Analysis of Body Fluids in Clinical Chemistry. 2nd ed., 2018.** This guideline provides information for the medical laboratory for evaluating measurement procedures, as well as a strategy to characterize assay performance, when applied to body fluid matrixes. Key concepts that apply to the entire test cycle, including preexamination, examination, and postexamination phases of body fluid testing, are discussed.

EP05 **Evaluation of Precision of Quantitative Measurement Procedures. 3rd ed., 2014.** This document provides guidance for evaluating the precision performance of quantitative measurement procedures. It is intended for manufacturers of quantitative measurement procedures and for laboratories that develop or modify such procedures.

EP06 **Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach. 1st ed., 2003.** This document provides guidance for characterizing the linearity of a method during a method evaluation; for checking linearity as part of routine quality assurance; and for determining and stating a manufacturer's claim for linear range.

EP07 **Interference Testing in Clinical Chemistry. 3rd ed., 2018.** This guideline provides background information, guidance, and experimental procedures for investigating, identifying, and characterizing the effects of interferents on clinical chemistry test results.

EP09 **Measurement Procedure Comparison and Bias Estimation Using Patient Samples. 3rd ed., 2018.** This guideline covers the design of measurement procedure comparison experiments using patient samples and subsequent data analysis techniques to determine the bias between two *in vitro* diagnostic measurement procedures.

EP12 **User Protocol for Evaluation of Qualitative Test Performance. 2nd ed., 2008.** This document provides a consistent approach for protocol design and data analysis when evaluating qualitative diagnostic tests. Guidance is provided for both precision and method-comparison studies.

EP14 **Evaluation of Commutability of Processed Samples. 3rd ed., 2014.** 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.

EP15 **User Verification of Precision and Estimation of Bias. 3rd ed., 2014.** This document describes the estimation of imprecision and of bias for clinical laboratory quantitative measurement procedures using a protocol that can be completed within as few as five days.

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

Related CLSI Reference Materials (Continued)

EP17 **Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures. 2nd ed., 2012.** This document provides guidance for evaluation and documentation of the detection capability of clinical laboratory measurement procedures (ie, limits of blank, detection, and quantitation), for verification of manufacturers' detection capability claims, and for the proper use and interpretation of different detection capability estimates.

EP34 **Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking. 1st ed., 2018.** It is often medically necessary to provide results for specimens with concentrations above the analytical measuring interval of an *in vitro* diagnostic measurement procedure. This guideline helps manufacturers and laboratory scientists with establishing, validating, or verifying a dilution scheme that will provide an extended measuring interval for such specimens.

GP34 **Validation and Verification of Tubes for Venous and Capillary Blood Specimen Collection. 1st ed., 2010.** This document provides guidance for conducting validation and verification testing for venous and capillary blood collection tubes.

GP44 **Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests. 4th ed., 2010.** This document includes criteria for preparing an optimal serum or plasma sample and for the devices used to process blood specimens.

M29 **Protection of Laboratory Workers From Occupationally Acquired Infections. 4th ed., 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.

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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

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

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

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