EP26-A
User Evaluation of Between-Reagent Lot Variation; Approved Guideline

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.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.
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For further information on committee participation or to submit comments, contact CLSI.

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Abstract

Clinical and Laboratory Standards Institute document EP26-A—User Evaluation of Between-Reagent Lot Variation; Approved Guideline provides guidance for laboratories on the evaluation of a new reagent lot, including a protocol that uses patient samples to detect significant changes from the current lot. Guidance is provided on establishing what lot-to-lot difference is significant and whether the observed difference is acceptable based on the established criteria. If the initial evaluation indicates a clinically significant difference, then appropriate follow-up studies and actions are also discussed. The protocol attempts to balance the need to reliably detect clinically significant change in reagent performance that may affect patient results with the recognition that reagent lot verification is a relatively frequent task that puts demands on the laboratory’s limited resources.


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Foreword

Changes in measurement procedure performance may occur with a change in reagent lot. Possible causes include changes in reagent component materials, instability of a component in a reagent, damage in transportation or storage, or incorrect calibration of the new reagent lot. Consequently, it is good laboratory practice to verify the consistency of patient sample results when introducing a new lot of reagents.

A shift in the results obtained with QC samples may be observed with a new lot of reagents. These changes in QC results are often caused by a difference in the interaction of the QC material being tested with the current and new reagent lots, commonly referred to as a matrix effect, while there is actually no change in the performance of the measurement procedure as measured with patient sample results.\(^1\)

It is also possible that a reagent lot–related change in measurement procedure performance may impact patient sample results with little or no apparent impact on QC sample results. In such instances, an insignificant change in QC material results from one reagent lot to the next could mask a significant change in patient sample results.

This document provides a systematic approach for detecting significant changes in measurement procedure performance for patient samples due to reagent lot changes, and for confirming that patient sample results are consistent between two reagent lots.

Key Words

Commutability, matrix bias, matrix effect, quality control, reagent
User Evaluation of Between-Reagent Lot Variation; Approved Guideline

1 Scope

This guideline provides a simple, practical, and statistically sound protocol to evaluate the consistency of patient sample results when a new analytical reagent lot replaces a reagent lot currently in use. This document is designed primarily for use with quantitative measurement procedures, but the same principles can be applied to measurement procedures that provide a clinically qualitative result based on a supplied quantitative measurement. This guideline is not intended for use with measurement procedures that only provide qualitative results. This guideline is intended for use in the clinical laboratory and is designed to work within the practical limitations that exist in that environment.

This guideline is not intended to provide detailed procedures for reagent manufacturers. The needs of reagent lot-to-lot testing by manufacturers, and the resources available, are different from those of the clinical laboratory. However, reagent manufacturers may use this document to understand the types of verification studies that may be performed in their customers’ laboratories.

2 Introduction

The potential for a change in performance with a new reagent lot has been shown for both QC and patient samples and is recognized by regulatory and accreditation organizations that have incorporated verification of the performance of a new reagent lot into their recommendations for good laboratory practice.

The goal of both reagent manufacturers and clinical laboratories is to provide accurate patient results. Reagent manufacturers use a number of procedures to validate the performance of a new reagent lot during the manufacturing process. Reagents are released only when the performance criteria are met. Manufacturers may have information regarding expected consistency of patient sample results when introducing a new lot of reagents as established internally or at other laboratories.

Even though reagent performance was validated by the manufacturer before release, the laboratory needs to verify that the new reagent lot, as received, meets the laboratory’s clinical performance needs. Possible causes of a change in performance with a new reagent lot include:

- Changes in reagent component materials
- Instability of a component in a reagent
- Reagents compromised in transportation or storage
- Incorrect calibration of the new reagent lot

Verifying that these potential changes have not occurred is important to assure the quality of laboratory results.

Between-reagent lot variation can affect results for QC materials, patient samples, or both. For some measurement procedures, reagent lot variation is observed in results for QC products when there has not been a significant change in patient sample results. A systematic change in QC results may not be immediately apparent, but may become recognized only after a number of QC results have been accumulated over a period of time while using a new reagent lot. This variation for QC results is often ascribed to “matrix effects,” which suggests that the QC material is not commutable with fresh patient samples. This noncommutability is not surprising because the manufacturing process for QC materials has a significant impact on the matrix of these samples and the reagent manufacturer’s first concerns must be accuracy and consistency with patient sample results. However, it cannot be assumed that the absence
of a lot-to-lot difference in the results obtained from QC samples is proof that no such difference exists with patient samples. It is possible that a difference in patient sample results occurs between two different reagent lots, but there is no difference seen for QC results. This situation may occur because the magnitude of matrix-related differences for the QC material is different for each reagent lot and the differences may offset each other to appear as if no change has occurred when a change exists for patient samples. Such a difference in patient results will not be detected if only QC materials are used during crossover testing when reagent lots are changed. In addition, QC material supplied with the reagents may be “optimized” to perform correctly with each new reagent lot. In that circumstance, performance of the new reagent lot with the supplied QC material may not reflect performance with patient samples.

Therefore, it is important that the potential risk for erroneous patient results associated with a new reagent lot be assessed, and reagent lot-to-lot evaluations be performed using patient samples for all reagent lot changes. This assessment should occur before, or concurrent with, initial use of the new reagent lot for patient testing.

The verification by the laboratory of performance of new reagent lots for use is a time-limited procedure and can be complicated by a variety of issues. The evaluating laboratory must have access to adequate numbers of appropriate clinical samples for evaluation, sufficient instrument and technologist time for the evaluation, and sufficient stock of previously verified reagents so that the verification procedure is not emergent. In addition, laboratory management must define the acceptable limits for patient results when changing a lot of a reagent for all of the measurement procedures that are being evaluated.

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 blood-borne 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.17 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 M29.28

4 Terminology

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.
The Quality Management System Approach

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

<table>
<thead>
<tr>
<th>Organization</th>
<th>Personnel</th>
<th>Process Management</th>
<th>Nonconforming Event Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Customer Focus</td>
<td>Purchasing and Inventory</td>
<td>Documents and Records</td>
<td>Assessments</td>
</tr>
<tr>
<td>Facilities and Safety</td>
<td>Equipment</td>
<td>Information Management</td>
<td>Continual Improvement</td>
</tr>
</tbody>
</table>

EP26-A addresses the QSE indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

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.

EP26-A does not address any of the clinical laboratory path of workflow steps. For a description of the document listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.
Related CLSI Reference Materials


EP05-A2 Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition (2004). This document provides guidance for designing an experiment to evaluate the precision performance of quantitative measurement methods; recommendations on comparing the resulting precision estimates with manufacturers’ precision performance claims and determining when such comparisons are valid; as well as manufacturers’ guidelines for establishing claims.

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.

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 assist assay manufacturers and laboratorians in the appropriate use of these materials for calibration and trueness assessment of in vitro diagnostic medical devices.

EP31-A-IR Verification of Comparability of Patient Results Within One Health Care System; Approved Guideline (Interim Revision) (2012). This document provides guidance on how to verify comparability of quantitative laboratory results for individual patients within a health care system.

GP44-A4 Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guideline—Fourth Edition (2010). This document includes criteria for preparing an optimal serum or plasma sample and for the devices used to process blood specimens.

M29-A3 Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005). 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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