CLINICAL AND LABORATORY STANDARDS INSTITUTE®

2nd Edition

EP26

User Evaluation of Acceptability of a Reagent Lot Change

This guideline includes recommendations for laboratories on evaluating a new reagent lot, based on a protocol that uses patient samples to detect clinically important changes from the current lot.

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

EP26-Ed2
April 2022
Replaces EP26-A

User Evaluation of Acceptability of a Reagent Lot Change

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Abstract

Clinical and Laboratory Standards Institute guideline EP26—*User Evaluation of Acceptability of a Reagent Lot Change* provides recommendations for laboratories on evaluating a new reagent lot, based on a protocol that uses patient samples to detect clinically important changes from the current lot. It provides guidance on determining whether lot-to-lot differences are significant and whether an observed difference is acceptable based on the established criteria. The protocol attempts to balance the need to detect changes in reagent performance that may adversely affect patient results with the fact that reagent lot verification is a relatively frequent task that places demands on the laboratory's limited resources. The more extensive initial setup of the protocol at the individual site is a one-time task performed in advance, making the subsequent testing of new reagent lots a straightforward procedure.

Clinical and Laboratory Standards Institute (CLSI). *User Evaluation of Acceptability of a Reagent Lot Change*. 2nd ed. CLSI guideline EP26 (ISBN 978-1-68440-137-6 [Print]; ISBN 978-1-68440-138-3 [Electronic]). Clinical and Laboratory Standards Institute, USA, 2022.

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Suggested Citation

CLSI. *User Evaluation of Acceptability of a Reagent Lot Change*. 2nd ed. CLSI guideline EP26. Clinical and Laboratory Standards Institute; 2022.

Previous Edition:
September 2013

EP26-Ed2

ISBN 978-1-68440-137-6 (Print)

ISBN 978-1-68440-138-3 (Electronic)

ISSN 1558-6502 (Print)

ISSN 2162-2914 (Electronic)

Volume 42, Number 11

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Foreword

A change in reagent lot may lead to changes in measurement procedure performance. Possible causes of this phenomenon include changes in reagent component materials, instability of a component in a reagent, damage during 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 a new reagent lot is introduced.

Historically, testing of QC samples has often been used as a primary tool to verify new reagent lot performance. However, although testing QC samples is key to monitoring measurement procedure performance over time, it may not be a reliable indicator of lot-to-lot consistency for all measurement procedures. A new reagent lot may lead to a shift in the results obtained with QC samples. These changes in QC results are often caused by a difference in the interaction of the QC material with the current vs new reagent lots, commonly referred to as a matrix effect, although there is no change in the measurement procedure performance as measured with patient sample results. It is also possible for a reagent lot–related change in measurement procedure performance to affect patient sample results with little or no apparent effect on QC sample results. In such instances, an insignificant change in QC results from one reagent lot to the next could mask a significant change in patient sample results.

This guideline describes 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.

Overview of Changes

This guideline replaces the previous edition of the approved guideline, EP26-A, published in 2013. Several changes were made in this edition, including:

- More clearly delineating the two stages of the protocol to clarify that the setup stage is performed only once, before any new reagent lot evaluations
- Providing additional detail about the statistical techniques used, so that the included tables can be extended as needed
- Revising discussion of allowable total analytical error (TEa) as a basis for determining critical difference (CD) to align with current recommendations and to improve clarity regarding the relationship between the CD and TEa
- Expanding the examples of reagent lot change evaluation to provide more detail on determining the CD and other critical parameters

This guideline describes a practical approach for screening new reagent lots for clinically significant performance changes with patient samples. This protocol is designed to use a small number of samples. Thus, lots can be screened quickly with limited resources. The protocol consists of two stages:

- **Stage 1** sets up the protocol for each analyte. This stage involves making decisions about the medically acceptable differences caused by reagent lot change and the acceptable risks associated with incorrect inferences. However, this stage can be performed before any reagent lots are evaluated.
- **Stage 2** is the evaluation of a new reagent lot, using the protocol developed in stage 1. This stage is simple and rapid and is performed for every new reagent lot.

Additionally, the process described enables the laboratory to determine the effectiveness of the protocol used, including the expected probability of detecting a significant lot-to-lot difference and the probability of falsely rejecting an acceptable lot. The process also shows how factors such as measurement procedure imprecision and choice of CD affect the effectiveness and practicality of the chosen protocol. No single fixed protocol is appropriate for all measurement procedures. Therefore, this guideline provides recommendations on developing specific protocols.

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

Commutability
Critical difference
Matrix effect
Matrix-related bias
Quality control
Reagent lot

User Evaluation of Acceptability of a Reagent Lot Change

1 Introduction

1.1 Scope

This guideline describes a statistically sound protocol for evaluating the consistency of patient sample results when a new analytical reagent lot replaces a reagent lot currently in use. It is designed for use with quantitative measurement procedures, and more generally for measurement procedures that report on a continuous scale. The same principles can be applied to measurement procedures that convert results from a continuous scale to a qualitative report based on a cutoff value. This guideline is intended for use in the medical laboratory and is designed to work within the practical limitations of that environment.

This guideline is not intended for use with measurement procedures that provide only qualitative or semiquantitative results. It is also not intended for measurement procedures for which a shift in patient results is expected with new reagent lots. For some measurement procedures, a shift in patient results with a new reagent lot is usual and expected, because the reagents are biological materials that may have lot-to-lot differences. Such measurement procedures include prothrombin time and activated partial thromboplastin time. The usual processes for clinical use of these measurement procedures account for this expected difference, and new lot evaluation as described in this guideline is not necessary or useful. Guidance for these measurement procedures provides detail on handling reagent lot changes. See CLSI documents H47[1] and H54.[2]

Additionally, this guideline is not intended to describe procedures for reagent manufacturers. The requirements of reagent lot-to-lot testing by manufacturers, as well as the resources available, are different from those of the medical laboratory. However, reagent manufacturers may use this guideline to understand the types of verification studies that may be performed in their customers' laboratories.

1.2 Background

The potential for a change in performance with a new reagent lot has been shown for both QC and patient samples. This possibility is recognized by regulatory and accreditation organizations, which have incorporated verification of the performance of a new reagent lot into their recommendations for good laboratory practice.[3-11]

The goal of both reagent manufacturers and medical laboratories is to provide accurate patient results. Reagent manufacturers use several procedures to validate the performance of a new reagent lot during the manufacturing process. Reagents are available to medical laboratories only when the performance criteria are met. As part of the overall quality process, manufacturers may compile information on the expected lot-to-lot consistency of patient sample results, as established internally or at other laboratories. However, because of differences in the study designs used, the manufacturer's protocols and acceptance criteria for lot-to-lot variability may not be applicable for medical laboratories. Specific acceptability limits apply only to the associated protocol for which the limits were developed. Therefore, this guideline focuses on establishing a critical difference (CD), which is based on an acceptability limit defined by the laboratory according to the measurement procedure's clinical use.

CD/S_{WRL}	S_r/S_{WRL}	RL for Mean Difference									
		0.90 • CD		0.80 • CD		0.70 • CD		0.60 • CD		0.55 • CD	
		Power	N	*Power*	N	*Power*	N	*Power*	N	*Power*	N
1.5	1.00	0.594	5	0.698	6	0.800	7	0.910	10	0.951	12
1.5	0.95	0.588	7	0.692	11	0.800	20	0.904	114	—	—

Statistical power (true rejection rate, 1 – β or 1 – false acceptance rate)

Number of samples to be tested

Abbreviations: CD, critical difference; N, number of samples; RL, rejection limit; S_r, repeatability; S_{WRL}, within–reagent lot imprecision.
Symbol: β, probability of making a false lot acceptance for a single concentration level.

Figure 5. Interpretation of Tables A1 to A3 in Appendix A Entries

To use Tables A1 to A3 in Appendix A, the laboratory needs to know the ratio of the CD to the measurement procedure's S_{WRL} (CD/S_{WRL} in the first column) and the ratio of the measurement procedure's S_r to its S_{WRL} (S_r/S_{WRL} in the second column). The S_r, S_{WRL}, and CD must be applicable to the set of samples tested at a given target concentration interval. If two (or more) sets of samples will be tested at two (or more) target concentration intervals, the appropriate S_r, S_{WRL}, and CD for each target concentration interval need to be available. The laboratory director should:

1. Locate the measurement procedure's CD/S_{WRL} in the first column.
2. Locate the measurement procedure's S_r/S_{WRL} from the rows in the second column that correspond to the ratio in step 1.
3. Move across the row from the cell located in step 2 until the number in the "*Power*" column is greater than or equal to the desired "*Power*" (typically 0.80 or 0.90). The number in the adjacent "N" column is the number of samples that needs to be tested with each reagent lot at a specified target concentration interval to detect a difference greater than or equal to the CD.

5.1.1.2 Example of Using Table A1 in Appendix A

For the measurand in question, the laboratory wants to achieve a statistical power of at least 90% (meaning that the probability of not detecting a clinically unacceptable difference between lots is no more than 10%). The CD/S_{WRL} is 3.0. The S_r/S_{WRL} is 1.00. The laboratory plans to evaluate the reagent lot at a single measurand concentration. Figure 6 illustrates this example. The laboratory director should start at the left-hand column (CD/S_{WRL}) and go down to the row that contains a CD/S_{WRL} ratio of 3.0 in the first column and an S_r/S_{WRL} ratio of 1.00 in the second column. The columns labeled "*Power*" indicate the statistical power achievable using the number of samples in the adjacent "N" column (to the right of the "*Power*" column). In this example, the "*Power*" column under the "0.60 • CD" heading indicates that the *Power* is 0.929. The corresponding cell indicates that the number of patient samples that needs to be tested to achieve this statistical power is three. Finally, the laboratory director should go up the column containing this cell to find that it needs to use an RL 0.60 times the CD to achieve the desired statistical power.

7 Examples of Evaluating Between-Lot Shifts Using Patient Data

This chapter includes examples of the protocol applied to several representative analytes. The example analytes are glucose, aspartate transaminase (AST), sodium (Na), thyroid-stimulating hormone (TSH), and high-density lipoprotein (HDL) cholesterol. Subchapters 7.1.1 and 7.1.2 summarize the process used in stage 1. Subchapter 7.1.3 discusses the details for each individual analyte. Calculations for glucose and HDL cholesterol are presented in both mg/dL and mmol/L. The values are rounded to the commonly reported number of significant digits. Because of different rounding, the results obtained using one set of units may not exactly match those that use the other set of units at every step. The examples are designed to be consistent within one set of units and to result in the same protocol for that analyte. Hence, intermediate results may not convert exactly between mg/dL and mmol/L. Although intermediate results are rounded when displayed in the examples, unrounded values are used for subsequent calculations.

7.1 Stage 1: Setup

7.1.1 Determining Key Parameters

The first step is to determine the key parameters: target concentration(s) (based on medical decision concentrations), CD at each concentration, S_{WRL}, and S_r. The S_{WRL} and S_r values are obtained from the manufacturer's documentation of measurement procedure performance or in-house laboratory performance studies. Table 4 summarizes the relevant values. Using one or more of the approaches outlined in Subchapter 3.1, the laboratory director must determine CD values at each of the relevant target concentrations for each analyte. The examples provided in Subchapters 7.1.3.1 to 7.1.3.5 illustrate the process of determining appropriate and practical CD values.

Table 4. Example Data for Glucose, AST, Na, TSH, and HDL Cholesterol

Analyte	Target Concentration	S_{WRL}	S_r	S_r/S_{WRL}
Glucose, mmol/L	2.8	0.05	0.03	0.60
	8.3	0.11	0.08	0.73
	16.6	0.25	0.19	0.76
Glucose, mg/dL	50	1.0	0.6	0.60
	150	2.1	1.5	0.71
	300	4.5	3.5	0.78
AST, IU/L	40	1.3	0.8	0.62
	200	4.1	1.3	0.32
Na, mmol/L	140	1.0	0.7	0.70
TSH, mIU/L	0.35	0.018	0.009	0.50
	5.4	0.20	0.16	0.80
HDL cholesterol, mmol/L	1.24	0.024	0.014	0.58
HDL cholesterol, mg/dL	48	0.9	0.5	0.56

Abbreviations: AST, aspartate transaminase; HDL, high-density lipoprotein; Na, sodium; S_r, repeatability; S_{WRL}, within–reagent lot imprecision; TSH, thyroid-stimulating hormone.

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PRINT ISBN 978-1-68440-137-6

ELECTRONIC ISBN 978-1-68440-138-3

EP26-Ed2