Evaluation of Stability of *In Vitro* Diagnostic Reagents; Approved Guideline

This document provides guidance for establishing shelf-life and in-use stability claims for *in vitro* diagnostic reagents such as reagent kits, calibrators, and control products.

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

Clinical and Laboratory Standards Institute document EP25-A—*Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline* provides guidance and regression-based procedures for establishing stability-related claims of *in vitro* diagnostic (IVD) reagents such as reagent kits, calibrators, control products, and sample diluents. This guideline was written primarily for manufacturers and regulatory agencies, but will also be of interest to clinical laboratories. It provides information on the design, implementation, data analysis, and documentation needs for studies to establish and verify shelf life and in-use life of IVD reagents. Additional topics address assessment of product transport conditions on stability and accelerated stability testing.


The Clinical and Laboratory Standards Institute consensus process, which is the mechanism for moving a document through two or more levels of review by the health care community, is an ongoing process. Users should expect revised editions of any given document. Because rapid changes in technology may affect the procedures, methods, and protocols in a standard or guideline, users should replace outdated editions with the current editions of CLSI/NCCLS documents. Current editions are listed in the CLSI catalog and posted on our website at www.clsi.org. If your organization is not a member and would like to become one, and to request a copy of the catalog, contact us at: Telephone: 610.688.0100; Fax: 610.688.0700; E-Mail: customerservice@clsi.org; Website: www.clsi.org
Foreword

Stability of an in vitro diagnostic (IVD) reagent reflects its ability to maintain consistent performance characteristics over time. Unlike precision, bias, and other common performance attributes, product stability is rarely assessed directly by customer testing. As such, there is increased burden on manufacturers to ensure that stability claims are developed from experimental designs and data analyses that are appropriate for each product’s particular requirements and applications.

IVD reagents, in the context of this guideline, represent end-use consumable products sold for the purpose of performing clinical measurements on patient specimens or other samples. Examples of such products are IVD reagent kits and their associated calibrators, controls, sample diluents, and system generic reagents.

Content of this guideline is aligned with European Standard EN 13640:2002—Stability Testing of In Vitro Diagnostics Reagents, referenced herein as EN 13640. Two other important internationally recognized guidance documents relative to stability study design and analyses are International Conference on Harmonization (ICH) Q1A (R2) and ICH Q1E. Although these were developed for drugs and drug substances, much of their content is directly relevant to IVD reagents.

Key Words

Accelerated stability, allowable drift, calibration interval, expiration dating, in-use life, shelf life, stability monitoring, stability plan, transport simulation
Evaluation of Stability of *In Vitro* Diagnostic Reagents; Approved Guideline

1 Scope

This guidance document provides information on the establishment and verification of shelf-life and in-use stability claims for quantitative and qualitative *in vitro* diagnostic (IVD) reagents. It includes background information and typical content to consider when creating a stability testing plan for a particular product, logistics of performing the studies, recommended data analyses, and documentation of stability claims. Additional topics include assessment of product transport conditions on stability claims, stability monitoring (verification), and uses of accelerated stability testing.

The intended users of this guideline are primarily manufacturers of IVD reagents and regulatory agencies. Clinical laboratorians may find this information useful in interpreting commercial product stability claims, as well as for establishing stability attributes of “laboratory-developed test” methods.

This guideline does not address instrument systems, laboratory equipment, software, or patient samples. Stability testing of raw materials or components of reagent kits or consumables is not addressed explicitly. The principles described in this document could, however, be adapted by manufacturers toward that purpose.

2 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 infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the US Centers for Disease Control and Prevention.\(^5\) For specific precautions for preventing the laboratory transmission of all infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious disease, refer to CLSI document M29.\(^6\)

3 Terminology

3.1 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 of 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 focuses on harmonization of terms to facilitate the global application of standards.
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 approach is based on the model presented in CLSI document HS01—*A Quality Management System Model for Health Care*. 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>
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<tr>
<th>Documents and Records</th>
<th>Organization</th>
<th>Personnel</th>
<th>Equipment</th>
<th>Purchasing and Inventory</th>
<th>Process Control</th>
<th>Information Management</th>
<th>Occurrence Management</th>
<th>Assessments—External and Internal</th>
<th>Process Improvement</th>
<th>Customer Service</th>
<th>Facilities and Safety</th>
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EP25-A addresses the QSEs 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.

Adapted from CLSI document HS01—*A Quality Management System Model for Health Care*. 
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-A2 Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (2002). This document addresses procedures for determining the bias between two clinical methods, and the design of a method comparison experiment using split patient samples and data analysis.


EP14-A2 Evaluation of Matrix Effects; Approved Guideline—Second Edition (2005). This document provides guidance for evaluating the bias in analyte measurements that is due to the sample matrix (physiological or artificial) when two measurement procedures are compared.

EP15-A2 User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (2005). 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.

EP17-A Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (2004). This document provides guidance for determining the lower limit of detection of clinical laboratory methods, for verifying claimed limits, and for the proper use and interpretation of the limits.

EP18-A Quality Management for Unit-Use Testing; Approved Guideline (2002). This guideline recommends a quality management system for unit-use devices that will aid in the identification, understanding, and management of sources of error (potential failure modes) and help to ensure correct results. It is targeted for those involved in the supervision of laboratory-testing quality management, and it addresses issues related to specimen collection through reporting of test results.

EP19-R A Framework for NCCLS Evaluation Protocols; A Report (2002). This document describes the different types of performance studies that are conducted to evaluate clinical assays.

EP21-A Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline (2003). This document provides manufacturers and end users with a means to estimate total analytical error for an assay. A data collection protocol and an analysis method that can be used to judge the clinical acceptability of new methods using patient specimens are included. These tools can also monitor an assay’s total analytical error by using quality control samples.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.
Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots; Approved Guideline (1995). This document provides a protocol for evaluating the accuracy of a test to discriminate between two subclasses of subjects where there is some clinically relevant reason to separate them. In addition to the use of ROC plots, the importance of defining the question, selecting the sample group, and determining the “true” clinical state are emphasized.

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.