CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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EP25-A

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.

Clinical and Laboratory Standards Institute

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For further information on committee participation or to submit comments, contact CLSI.

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

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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.

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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.

3.2 Definitions

accelerated stability testing – a stability study designed to increase the rate of chemical or physical degradation of an IVD reagent by using exaggerated environmental conditions (eg, light, temperature, humidity); **NOTE:** Results from such studies may be used to compare the influence of product design/packaging factors or, in some cases, to estimate the expiration date when the product is handled under recommended storage conditions.

allowable drift – the maximum change in the quantity value by which product performance is kept within limits specified by the manufacturer.

Arrhenius equation – a mathematical function that describes the approximate relationship between the rate constant of a chemical reaction and the reaction temperature and energy of activation.

bias (of measurement) – estimate of a systematic measurement error (ISO/IEC Guide 99).[7]

calibration – operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication (ISO/IEC Guide 99)[7]; **NOTE 1:** Calibration should not be confused with adjustment of a measuring system, often mistakenly called 'self-calibration,' nor with verification of calibration (ISO/IEC Guide 99)[7]; **NOTE 2:** Calibration is the set of operations that establish, under specified conditions, the relationship between reagent system/instrument response and the corresponding concentration/activity values of an analyte.[8]

calibration interval – period of time following a calibration during which an IVD reagent under specified conditions demonstrates apparent change in measurand content within the allowable drift limit and all stability-related criteria are met.

design input requirements – the physical and performance requirements of a device that are used as a basis for device design.

environmental factors – variables that might affect the performance or efficacy of IVD reagents (eg, temperature, airflow, humidity, light).

expiration (expiry) date – upper limit of the time interval during which the performance characteristics of a material stored under specified conditions can be assured; **NOTE:** Expiry dates are assigned to IVD reagents, calibrators, control materials, and other components by the manufacturer based on experimentally determined stability properties (adapted from EN 375:2001, §3.6).[9]

first-order kinetics degradation – a product degradation reaction rate that can be described by a linear differential equation, leading to an exponential relationship between the product concentration and the reaction time.

in-use stability – duration of time over which the performance of an IVD reagent within its expiration date remains within specified limits after opening the container system supplied by the manufacturer, and put into use under standard operation conditions (eg, storage on the instrument).

***in vitro* diagnostic medical device (IVD medical device)** – a device, whether used alone or in combination, intended by the manufacturer for the *in vitro* examination of specimens derived from the human body to provide information for diagnostic, monitoring, or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles (GHTF/SG1/N045:2008).[10]

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:

Documents and Records	Equipment	Information Management	Process Improvement
Organization	Purchasing and Inventory	Occurrence Management	Customer Service
Personnel	Process Control	Assessments—External and Internal	Facilities and Safety

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.

Documents and Records	Organization	Personnel	Equipment	Purchasing and Inventory	Process Control	Information Management	Occurrence Management	Assessments—External and Internal	Process Improvement	Customer Service	Facilities and Safety
					X EP05 EP06 EP07 EP09 EP10 EP12 EP14 EP15 EP17 EP18 EP19 EP21 GP10 M29		EP18	EP18	EP07 EP10 EP18		M29

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.

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.

EP07-A2 **Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition (2005).** This document provides background information, guidance, and experimental procedures for investigating, identifying, and characterizing the effects of interfering substances on clinical chemistry test results.

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.

EP10-A3 **Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition (2006).** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of a measurement procedure or device.

EP12-A2 **User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline—Second Edition (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-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.

GP10-A **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.

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.

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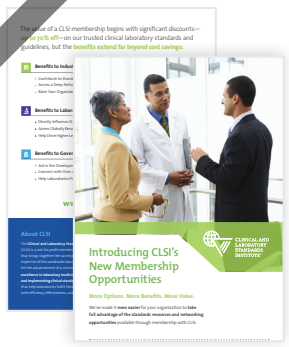

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