EP25-P
Vol. 28 No. 32

# Evaluation of Stability of *In Vitro* Diagnostic Method Products; Proposed Guideline

*PLEASE*

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This proposed document is published for wide and thorough review in the new, accelerated Clinical and Laboratory Standards Institute (CLSI) consensus-review process. The document will undergo concurrent consensus review, Board review, and delegate voting (ie, candidate for advancement) for 60 days.

Please send your comments on scope, approach, and technical and editorial content to CLSI.

Comment period ends

2 February 2009

The subcommittee responsible for this document will assess all comments received by the end of the comment period. Based on this assessment, a new version of the document will be issued. Readers are encouraged to send their comments to Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA; Fax: +610.688.0700, or to the following e-mail address: standard@clsi.org.

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*COMMENT*

This document provides guidance for establishing shelf-life and in-use stability claims for *in vitro* diagnostic method products 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

*Advancing Quality in Health Care Testing*

Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) is an international, interdisciplinary, nonprofit, standards-developing, and educational organization that promotes the development and use of voluntary consensus standards and guidelines within the health care community. It is recognized worldwide for the application of its unique consensus process in the development of standards and guidelines for patient testing and related health care issues. Our process is based on the principle that consensus is an effective and cost-effective way to improve patient testing and health care services.

In addition to developing and promoting the use of voluntary consensus standards and guidelines, we provide an open and unbiased forum to address critical issues affecting the quality of patient testing and health care.

## PUBLICATIONS

A document is published as a standard, guideline, or committee report.

**Standard** A document developed through the consensus process that clearly identifies specific, essential requirements for materials, methods, or practices for use in an unmodified form. A standard may, in addition, contain discretionary elements, which are clearly identified.

**Guideline** A document developed through the consensus process describing criteria for a general operating practice, procedure, or material for voluntary use. A guideline may be used as written or modified by the user to fit specific needs.

**Report** A document that has not been subjected to consensus review and is released by the Board of Directors.

## CONSENSUS PROCESS

The CLSI voluntary consensus process is a protocol establishing formal criteria for:

- the authorization of a project
- the development and open review of documents
- the revision of documents in response to comments by users
- the acceptance of a document as a consensus standard or guideline.

Most documents are subject to two levels of consensus—"proposed" and "approved." Depending on the need for field evaluation or data collection, documents may also be made available for review at an intermediate consensus level.

**Proposed** A consensus document undergoes the first stage of review by the health care community as a proposed standard or guideline. The document should receive a wide and thorough technical review, including an overall review of its scope, approach, and utility, and a line-by-line review of its technical and editorial content.

**Approved** An approved standard or guideline has achieved consensus within the health care community. It should be reviewed to assess the utility of the final document, to ensure attainment of consensus (ie, that comments on earlier versions have been satisfactorily addressed), and to identify the need for additional consensus documents.

Our standards and guidelines represent a consensus opinion on good practices and reflect the substantial agreement by materially affected, competent, and interested parties obtained by following CLSI's established consensus procedures. Provisions in CLSI standards and guidelines may be more or less stringent than applicable regulations. Consequently, conformance to this voluntary consensus document does not relieve the user of responsibility for compliance with applicable regulations.

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The comments of users are essential to the consensus process. Anyone may submit a comment, and all comments are addressed, according to the consensus process, by the committee that wrote the document. All comments, including those that result in a change to the document when published at the next consensus level and those that do not result in a change, are responded to by the committee in an appendix to the document. Readers are strongly encouraged to comment in any form and at any time on any document. Address comments to Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, PA 19087, USA.

## VOLUNTEER PARTICIPATION

Health care professionals in all specialties are urged to volunteer for participation in CLSI projects. Please contact us at customerservice@clsi.org or +610.688.0100 for additional information on committee participation.

EP25-P
ISBN 1-56238-684-0
Volume 28 Number 32
ISSN 0273-3099

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## Abstract

Clinical and Laboratory Standards Institute document EP25-P—*Evaluation of Stability of* In Vitro *Diagnostic Method Products; Proposed Guideline* provides guidance and regression-based procedures for establishing stability-related claims of IVD method products such as reagent kits, calibrators, control products, and sample diluents. This guideline was written primarily for manufacturers and regulatory agencies, but also will 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 method products. Additional topics address assessment of product transport conditions on stability and accelerated stability testing.

Clinical and Laboratory Standards Institute (CLSI). *Evaluation of Stability of* In Vitro *Diagnostic Method Products; Proposed Guideline*. CLSI document EP25-P (ISBN 1-56238-684-0). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2008.



**Suggested Citation**

(CLSI. *Evaluation of Stability of* In Vitro *Diagnostic Method Products; Proposed Guideline.* CLSI document EP25-P. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.)

**Proposed Guideline**
December 2008

ISBN 1-56238-684-0
ISSN 0273-3099

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## Foreword

Stability of an *in vitro diagnostic* (IVD) method product 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.

*In vitro* diagnostic method products, in the context of this guideline, represent end-use consumable products sold to laboratories for the purpose of performing clinical measurements on patient specimens or other samples. Examples of such products are method 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*[1]—referenced herein as EN 13640. Two other important internationally recognized guidance documents relative to stability study design and analyses are International Conference on Harmonisation (ICH) Q1A (R2)[2] and ICH Q1E.[3] While these were developed for drugs and drug substances, much of their content is directly relevant to IVD method products.[4]

### Invitation for Participation in the Consensus Process

An important aspect of the development of this and all CLSI documents should be emphasized, and that is the consensus process. Within the context and operation of CLSI, the term "consensus" means more than agreement. In the context of document development, "consensus" is a process by which CLSI, its members, and interested parties (1) have the opportunity to review and to comment on any CLSI publication; and (2) are assured that their comments will be given serious, competent consideration. Any CLSI document will evolve as will technology affecting laboratory or health care procedures, methods, and protocols; and therefore, is expected to undergo cycles of evaluation and modification.

The Area Committee on Evaluation Protocols has attempted to engage the broadest possible worldwide representation in committee deliberations. Consequently, it is reasonable to expect that issues remain unresolved at the time of publication at the proposed level. The review and comment process is the mechanism for resolving such issues.

The CLSI voluntary consensus process is dependent upon the expertise of worldwide reviewers whose comments add value to the effort. At the end of a 60-day comment period, each subcommittee is obligated to review all comments and to respond in writing to all which are substantive. Where appropriate, modifications will be made to the document, and all comments along with the subcommittee's responses will be included as an appendix to the document when it is published at the next consensus level.

### 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 Method Products; Proposed 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) method products. It includes background information to consider when creating a stability testing plan for a particular product, content of a stability plan, 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 method products 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, ISO, and CEN documents; and that legally required use of terms, regional usage, and different consensus timelines are all challenges to harmonization. In light of this, CLSI recognizes that harmonization of terms facilitates the global application of standards and deserves immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

### 3.2 Definitions

**accelerated stability testing** – a stability study designed to increase the rate of chemical or physical degradation of an IVD method product by using exaggerated environmental conditions (eg, temperature, light, humidity).