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Protocol for the Evaluation, Validation, and Implementation of Coagulometers; Approved Guideline

This document provides guidance and procedures to the end user and manufacturer for the selection, evaluation, validation, and implementation of a laboratory coagulometer.

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

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Protocol for the Evaluation, Validation, and Implementation of Coagulometers; Approved Guideline

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Abstract

Clinical and Laboratory Standards Institute document H57-A—*Protocol for the Evaluation, Validation, and Implementation of Coagulometers; Approved Guideline* provides guidance and procedures to the end user and manufacturer for the selection, evaluation, validation, and implementation of a laboratory coagulometer. Guidelines are given on the information that should be sought by the end user and manufacturer before acquisition. Included are guidelines for the procedures, specimens, reagents, and data analysis that may be used in the assessment of a coagulometer. This document addresses the differences in workload and range of tests offered by different laboratories, and this is reflected in the user assessment guidelines. Finally, guidance is given on implementation, including training, education, and interfacing.

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Contents

Contents (Continued)

Foreword

Before a coagulometer can be used for testing patient samples, it must receive a thorough evaluation by the purchasing laboratory or an independent expert center. The scope of the evaluation depends upon who is performing the evaluation; the availability of independent evaluation data; the range of tests performed by the laboratory undertaking the evaluation; and the range of samples available to the evaluating laboratory.

Coagulometers used in clinical laboratories have become increasingly complex, and the evaluation of such instruments is complicated and time consuming. In addition to the common screening tests (prothrombin time, activated partial thromboplastin time, thrombin clotting time, and Clauss fibrinogen assay), most coagulometers also perform chromogenic and immunoturbidimetric assays. Some analyzers may also have the capability to perform chemiluminescent assays. Existing evaluation guidelines are generally aimed at clinical chemistry analyzers, in which well-defined analytes, with well-documented reference materials/standards, are assayed and a range of suitable matrices is available. For the majority of coagulation tests, the activity of whole enzyme pathways is assessed; this can only be achieved with citrated plasma samples.

Newer trends in hemostasis testing and reagent/instrument manufacturing necessitate the development of an updated guideline for the evaluation of coagulometers. Early evaluation protocols tended to compare instrument performance to the manual clotting technique; although this remains the international reference method for PT/INR (World Health Organization [WHO] 1983), it has now largely disappeared from routine laboratories. Contemporary reagents are frequently developed exclusively for use with a given instrument and consequently are unsuitable for instruments employing other end-point detection methods. With this trend towards tailored reagent/instrument systems, there is a need for a more holistic outlook to instrument evaluation. This may be achieved by comparison against reference reagents and reference instruments, selected for their suitability to the instrument and reagents under evaluation.

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.

In order to align the usage of terminology in this document with that of ISO, the term *accuracy,* in its metrological sense, refers to the closeness of the agreement between the result of a (single) measurement and a true value of a measurand, and comprises both random and systematic effects. *Precision* is defined as the "closeness of agreement between independent test/measurement results obtained under stipulated conditions." As such, it cannot have a numerical value, but may be determined qualitatively as high, medium, or low. For its numerical expression, the term *imprecision* is used, which is the "dispersion of results of measurements obtained under specified conditions." In addition, different components of precision are defined in H57-A, primarily *repeatability,* ie, "the closeness of the agreement between results of successive measurements of the same measurand carried out under the same conditions of measurement"; while *reproducibility* describes "the closeness of agreement of results of measurements under changed conditions."

The term *measurand* (a particular quantity subject to measurement) is used in combination with the term *analyte* (component represented in the name of a measurable quantity) when its use relates to a biological fluid/matrix; the term *reportable range* when referring to "a set of values of measurands for which the error of a measuring instrument (test) is intended to lie within specified limits"; and the term *measurement procedure* is combined with *analytical method* for a set of operations used in the performance of particular measurements according to a given method.

All terms and definitions will be reviewed again for consistency with international use, and revised appropriately during the next scheduled revision of this document.

Key Words

Coagulation analyzer, coagulometer evaluation, comparability, efficiency assessment, implementation, performance validation, precision

Protocol for the Evaluation, Validation, and Implementation of Coagulometers; Approved Guideline

1 Scope

This guideline specifies recommendations on how to plan and execute the selection, evaluation, validation, and implementation of a laboratory coagulometer. It includes assessment of safety, carryover, precision, bias, linearity, and comparability for coagulometers that perform clotting, chromogenic and/or immunoturbidimetric and/or chemiluminescent testing on plasma. The intended users of this guideline are hospitals, reference laboratories, and manufacturers. It is intended as a guideline for evaluation of commercially available coagulometers that have received prior US Food and Drug Administration 510(k) clearance, CE mark, or other country-specific registration. This guideline is not intended for use by facilities evaluating point of care or manufacturers of point-of-care coagulometers. For information on point-of-care coagulometers, refer to CLSI/NCCLS document H49.[1] It also is not intended to provide guidance for platelet testing or the completion of 510(k) clearance documentation, nor intended to proscribe the level of customer service provided by vendors. This guideline recommends the selection of tests and procedures to validate the performance of coagulometers, but it does not address the process to validate each test method of the device. This guideline is not intended to replace any existing standards or requirements but should be used in addition to existing standards.

2 Introduction

This guideline details several different steps in the evaluation of a coagulometer by the end user and manufacturer. The evaluation of a coagulometer typically progresses from market research, where several desirable instrument platforms are selected, to a preliminary preacquisition evaluation of one or more instruments, to a more detailed postacquisition validation of a single platform, culminating in implementation of the testing system for clinical use. This guideline is intended to guide the end user and manufacturer through the evaluation, validation, and implementation stages of this process. Where applicable, the guideline has addressed separately the level of evaluation considered appropriate for low-volume hospital laboratories vs larger hospital or reference laboratories with a higher test volume and more complex test mix. For information on point-of-care coagulometers, refer to CLSI/NCCLS document H49.[1]

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 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.[2] 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.[3]

4 Definitions

accuracy (of measurement) – closeness of the agreement between the result of a measurement and a true value of the measurand (VIM93).[4]

activated partial thromboplastin time (APTT) – the time, in seconds, required for a fibrin clot to form in a plasma sample after appropriate amounts of calcium chloride, and a partial thromboplastin reagent (phospholipid plus a contact activator), have been mixed with the sample; **NOTE:** The APTT measures the intrinsic and common coagulation pathways.

analyte – component represented in the name of a measurable quantity (ISO 17511)[5]; **NOTE 1:** In the type of quantity "mass of protein in 24-hour urine," "protein" is the analyte. In "amount of substance of glucose in plasma," "glucose" is the analyte. In both cases, the long phrase represents the **measurand** (ISO 17511)[5]; **NOTE 2:** In the type of quantity "catalytic concentration of lactate dehydrogenase isoenzyme 1 in plasma," "lactate dehydrogenase isoenzyme 1" is the analyte (ISO 18153).[6]

analytical measurement range (AMR) – the range of test values that a method can directly measure on the specimen without any dilution, concentration, or other pretreatment not part of the usual assay process.

bias – the difference between the expectation of the test results and an accepted reference value (ISO 3534-1).[7]

calibration – set of operations that establish, under specified conditions, the relationship between values of quantities indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards (VIM93)[4]; **NOTE:** According to the US Code of Federal Regulations (CFR), calibration is the process of testing and adjustment of an instrument, kit, or test system, to provide a known relationship between the measurement response and the value of the substance being measured by the test procedure (42 CFR 493.1217).[8]

clinically reportable range (CRR) – the range of test values that a method can report as a quantitative result, allowing for specimen dilution, concentration, or other pretreatment used to extend the direct AMR; **NOTE 1:** For example, if it is desired to report a result that exceeds the AMR, the specimen is commonly diluted to bring the analyte into that range, the diluted specimen is reassayed, and the final result calculated using the dilution factor; **NOTE 2:** The establishment of the CRR is a medical judgment made by the laboratory director, and is based in part on the assay technology.

coagulometer//coagulation analyzer – an analytical instrument for measuring coagulation parameters

coefficient of variation (CV) – for a non-negative characteristic, the ratio of the standard deviation to the average (ISO 3534-1)[7]; **NOTE 1:** The ratio may be expressed as a percentage; **NOTE 2:** The term "relative standard deviation" is sometimes used as an alternative to "coefficient of variation" but this use is not recommended; **NOTE 3:** It is often multiplied by 100 and expressed as a percentage.

comparability – closeness of the agreement between the results of the coagulometer/reagent system under evaluation with an established method.

confidence interval – the computed interval with a given probability (eg, 95%) that the true value of a variable such as a mean, proportion, or rate is contained within the interval.

end user – personnel in the health care facility familiar with the medical device and its operation.

error (of measurement)//measurement error – the result of a measurement minus a true value (or accepted reference value) of the measurand (modified from VIM93).[4]

evaluation – generic term for any study that measures the performance capabilities of an assay.

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 the most current edition of CLSI/NCCLS document HS1—*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:

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

H57-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 & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessments—External & Internal	Process Improvement	Customer Service	Facilities & Safety
GP19	GP19	GP19	X GP19	GP19	X AUTO8 C28 EP5 EP7 EP9 EP10 EP15 GP19 H47 H54	GP19	GP19	X EP10	EP7 GP19	GP19	GP19

Adapted from CLSI/NCCLS document HS1—*A Quality Management System Model for Health Care*.

Path of Workflow

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, CLSI/NCCLS document GP26—*Application of a Quality Management System Model for Laboratory Services* defines a clinical laboratory path of workflow which consists of three sequential processes: preexamination, examination, and postexamination. All clinical laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

H57-A addresses the clinical laboratory path of workflow steps 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.

Preexamination				**Examination**			**Postexamination**	
Examination ordering	Sample collection	Sample transport	Sample receipt/processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
AUTO8			H47	H47	X H47		AUTO8	

Adapted from CLSI/NCCLS document HS1—*A Quality Management System Model for Health Care*.

Related CLSI Reference Materials*

AUTO8-A **Managing and Validating Laboratory Information Systems; Approved Guideline (2006).** This document provides guidance for developing a protocol for validation of the laboratory information system (LIS), as well as protocols for assessing the dependability of the LIS when storing, retrieving, and transmitting data.

C28-A2 **How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline—Second Edition (2000).** This document contains guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests.

EP5-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.

EP7-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.

EP9-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.

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 for completion 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.

GP19-A2 **Laboratory Instruments and Data Management Systems: Design of Software User Interfaces and End-User Software Systems Validation, Operation, and Monitoring; Approved Guideline—Second Edition (2003).** This document identifies important factors that designers and laboratory managers should consider when developing new software-driven systems and selecting software user interfaces. Also included are simple rules to help prepare validation protocols for assessing the functionality and dependability of software.

H21-A5 **Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays; Approved Guideline—Fifth Edition (2008).** This document provides procedures for collecting, transporting, and storing blood; processing blood specimens; storing plasma for coagulation testing; and general recommendations for performing the tests.

H47-A **One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin (APTT) Time Test; Approved Guideline (1996).** This document provides guidelines for performing the PT and APTT tests in the clinical laboratory, for reporting results, and for identifying sources of error.

H49-A **Point-of-Care Monitoring of Anticoagulation Therapy; Approved Guideline (2004).** This document provides guidance to users and manufacturers of point-of-care coagulation devices for monitoring heparin and warfarin anticoagulant therapy, and to ensure reliable results comparable to those obtained by routine clinical laboratory testing.

H54-A **Procedures for Validation of INR and Local Calibration of PT/INR Systems; Approved Guideline (2005).** This document describes the use of certified plasmas to enhance performance of the prothrombin time (PT)/International Normalized Ratio (INR) system test; reviews limitations of the INR system that may occur when a manufacturer-determined ISI is used without local verification or calibration; and provides a rationale for performing local ISI verification with recommendations as to when PT calibration may be indicated. Part I is a detailed, expanded account for manufacturers and Part II is an abbreviated version useful for the clinical laboratory.

* Proposed-level documents are being advanced through the Clinical and Laboratory Standards Institute consensus process; therefore, readers should refer to the most current editions.

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