A Framework for Using CLSI Documents to Evaluate Medical Laboratory Test Methods

Report
EP19-Ed3
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Replaces EP19-Ed2

Introduction

EP19 has been revised to ensure its accuracy as a reference guide for the use of CLSI documents to establish and implement test methods using the Test Life Phases Model. EP19 is not an evaluation protocol (EP) in the traditional sense. Rather, it is a report that references existing CLSI method evaluation documents, organized around the concept of the Test Life Phases Model.

In this report, all entities that create new test methods are referred to as "developers." In EP19, developers include both commercial manufacturers and laboratories that create new test methods or modify regulatory-cleared and -approved commercially available test methods in a way that could modify performance characteristics and/or change the intended use.

Although EP19 is intended to help users identify appropriate CLSI documents for the establishment and implementation of test methods, EP19 cannot cover every aspect of establishment and/or implementation for every circumstance. Some analytes, test methods, and/or specialties have unique requirements. For some test methods, special evaluations for which there are no available CLSI documents might be needed. Where appropriate, other resource citations that might be useful to the reader have been added.

To facilitate use of the most current editions of the CLSI documents for the establishment and implementation of test methods described in the Test Life Phases Model, EP19 introduces CLSI electronic product *Method Navigator*.[1] *Method Navigator*[1] enables users to easily access resources cited in the product, along with other helpful CLSI resources. CLSI electronic product *Method Navigator*[1] is meant to be used with EP19.

Overview of Changes

This report replaces the previous edition of the approved report EP19-Ed2, published in 2015. The original intent of EP19 to provide a useful, high-level guide has not changed. Several changes were made in this edition, including:

- Introducing CLSI electronic product *Method Navigator*[1]
- Updating the figures and flow chart
- Enhancing discussion of the concept of risk management as an integral part of the Test Life Phases Model
- Updating Special Cases section

Scope

EP19 is organized around the Test Life Phases Model, which is the concept that all test methods undergo establishment by a developer, followed by implementation by the end user, all sequentially. For the purposes of EP19, the term "test method" includes the processes, reagents, supplies, calibrators, control material, hardware, software, and any other components that make up a test. EP19 describes the considerations and processes for planning, performing, and documenting test method evaluations by referring users to the appropriate CLSI EP documents, along with other related documents and resources when applicable. Effective use of EP19 is based on the premise that both the developer and the end user have a QMS in place with appropriate controls over all essential processes, including personnel, environment, general processes, and documentation. Users should refer to CLSI electronic product *Method Navigator*[1] in conjunction with EP19.

Because CLSI documents are regularly updated, the EP documents can be considered generally accepted good practice for how test methods should be evaluated. EP19 provides general reference on the specific CLSI documents that are useful for test method evaluations and provides considerations for how users could most effectively benefit from this information. EP19 users should refer to the referenced CLSI documents for sufficient details to plan, perform, and interpret the evaluations correctly.

Intended User

EP19 is intended for use by medical laboratories, commercial manufacturers, and government agencies. The term "developer" is used in this report to include not only commercial manufacturers of regulatory-cleared and -approved test methods but also laboratories that develop their own test methods for implementation, which are commonly referred to as laboratory-developed tests (LDTs). Although commercial manufacturers are likely to have well-documented and approved protocols, EP19 is a resource for them, as well as for start-up companies. Laboratories that modify regulatory-cleared and -approved commercial test methods, eg, by changing reagents, sample volumes, or patient sample types or by adding analyte-specific reagents, are essentially creating a new test method. In these cases, the laboratory acting as the developer needs to establish acceptable performance characteristics, and the laboratory as the end user must verify performance as part of test method implementation.

The laboratory needs to establish performance characteristics when it is acting as a test method developer, regardless of whether it has recognized research and development facilities or is a medical laboratory that incorporates minor modifications to a test method or measuring system. Laboratories that create new test methods and those that make relatively minor changes to regulatory-cleared and -approved commercial test methods are considered developers and are responsible for establishing test method performance. EP19 is an especially useful resource for laboratories that are just beginning to use CLSI documents and those that use non–regulatory-approved or modified regulatory-cleared and -approved commercial test methods.

Background

The Test Life Phases Model as shown in the figure below categorizes test method evaluations into two major **stages:**

- Establishment of a test method by a developer
- Implementation of that established test method by an end user

Documentation of Decisions and Actions

Documentation provides objective evidence that requirements for establishing and implementing a new test method were met. Establishment Stage documentation includes the design plan, development record, test method procedure(s), validation plan with acceptance criteria, and validation record with decisions and signatures. Establishment Stage records include the data (eg, development, validation, calibration, QC) and the conclusions drawn from the data, such as those captured in summary reports. The developer could organize the Establishment Stage documentation by phase to make it easy for external assessors to reference how the test method was established.

Implementation Stage documents include the verification plan with acceptance criteria, procedure(s) used for the test method, results records, and summary records derived from the Preliminary Evaluation, Verification, and Launch Phases. The end-user laboratory should already have general procedures for what is needed during the Maintenance and Retirement Phases. Regulatory and accreditation requirements specify the retention periods of specific types of documents and records. The laboratory needs to retain all records associated with a test method and its related instruments and equipment according to applicable regulatory and accreditation requirements; however, in general, it is best to keep the documentation for at least two years after retiring the method from use. CLSI document QMS02[6] provides information about how to develop and manage laboratory policy, process, procedure, and form documents. CLSI document QMS26[7] provides information about how to manage laboratory records. CLSI electronic product *Method Navigator*[1] provides examples for the specific documentation needed as a test progresses through the Test Life Phases Model.

Risk Management

Risk management is a proactive process for identifying hazards, evaluating their associated risks, mitigating the risks when possible, and monitoring the effectiveness of the mitigation. Risk management is an integral part of the Test Life Phases Model and should be applied throughout the process. Well-documented risk management efforts during prelaunch phases are helpful for any investigations that occur after launch. For example, if a nonconformity occurs and erroneous patient results are released, information collected as part of risk management efforts can assist in developing an appropriate response. Additionally, any changes made to a test method, planned or unplanned, should trigger a risk assessment to ensure that risks to patient, operator, and environment have been considered. Laboratories should develop and maintain a detailed protocol for risk management and policies that apply to all laboratory operations holistically.

Although every test method is subject to hazards and/or failure during the preexamination, examination, and postexamination testing processes, the relative importance and likelihood of such hazards and failures varies with the test method and its intended use, the patient sample, the user, and the environment. The goal of risk management is to ensure that the test method is reliable, works as intended, and that any potential causes of harm to patients, operators, or the environment are identified and mitigated as much as is practicable. The risk management process consists of the following four stages:

- Risk assessment
- Risk control
- Risk management review
- Risk monitoring

Lack of a Primary Reference Test Method and/or Reference Material

In some cases, especially when test methods for novel measurands or for emerging pathogens are being developed, there might not be a closely related measurand, or any measurand, that can be used for comparison. In these cases, it could be necessary to compare the test method result with the disease state. It is also possible that the test method currently accepted as the primary reference test method (eg, microbiology culture) might not consistently correspond to the disease state. When diagnostic accuracy criteria and primary reference test methods do not exist, established evidence-based consensus diagnostic algorithms could be followed. Refer to the published literature[63,64] and CLSI document EP12[15] for additional information.

For quantitative test methods that do not have an international standard or otherwise quantified reference material, it might not be possible to determine numerical bias exactly. In these cases, test methods are developed using reference materials to which a nominal value has been assigned, based on mass spectrometry, electron microscopy, etc.; however, the reference material might not be universally used by all test method developers, and it might not have been evaluated for homogeneity, stability, commutability, QC, etc.[65] CLSI document MM03[31] discusses comparing a new molecular method with or without a primary reference test method. At times, a spiked recovery could be performed as an alternative method (see CLSI document EP34[26]).

Qualitative Test Methods

CLSI document EP12[15] provides the framework to determine or verify clinical sensitivity and specificity or PPA and NPA of qualitative test methods that yield binary results (positive/negative; present/absent) and appropriately assess agreement between qualitative test methods.

Many qualitative tests are based on an internal continuous response for which a cutoff value is established; one example is a sample-to-cutoff ratio in antibody tests. In these cases, this response can be used to measure test method performance such as LoD, imprecision, selectivity, and stability through quantitative techniques (see CLSI documents EP17,[16] EP05,[13] EP07,[24] and EP25,[18] respectively). CLSI document EP12[15] provides methods for assessing these performance metrics.

Multiplex Test Methods

Increasingly, molecular test methods are being designed to detect multiple analytes. These test methods present significant challenges when validation and verification studies are planned, performed, and evaluated. A significant burden for successful validation and verification studies arises when any of the measurands in the multiplex system fail to meet acceptance criteria because the other measurands as well as the calculated result used for clinical interpretation might be affected. CLSI document MM17[57] provides the framework for study designs, with attention to factors unique to multiplex test methods, such as acquisition of reference materials to include each analyte and complexity of data analysis. CLSI documents MM12[56] and MM22[62] discuss microarrays.

implementation – stage of the Test Life Phases Model; putting into service an instrument or test method by the end user for means of a definite plan or process.

imprecision – for quantitative test methods, dispersion of results of replicate measurements obtained under specified conditions; **NOTE:** It is expressed numerically as the standard deviation or the coefficient of variation.

intended use – use for which a product, process, or service is intended according to the specifications, instructions, and information provided by the manufacturer[8]; **NOTE:** The concept includes definition of the measurand, the target condition, and the clinical use of the test method, such as screening, diagnosis, prognosis, and/or monitoring of a target population or condition.

laboratory-developed test//laboratory-developed test method (LDT) – a type of test method that is designed, manufactured, and implemented for use within a single institution; **NOTE:** Regulatory agencies can consider modified regulatory-cleared and -approved commercial test methods LDTs.

launch – a phase in the Implementation Stage of the Test Life Phases Model. The first day patient samples are tested and results are reported for health care or other purposes using a test method verified by the end user.

maintenance – a phase in the Implementation Stage of the Test Life Phases Model. This phase includes all processes performed to keep a measuring system operational, including demonstration of acceptable performance using quality control, proficiency testing, and other regular activities associated with routine use; **NOTE 1:** Microbiologists often refer to this ongoing activity as "validation"; **NOTE 2:** Maintenance should not be confused with calibration verification (an ongoing regulatory requirement) that takes place in this phase.

matrix effect – influence of a property of the sample, other than the measurand, on the measurement of the measurand according to a specified test method and thereby on its measured value.[65]

measurand – quantity intended to be measured[67]; **EXAMPLE 1:** The "mass of protein in 24-hour urine from a given person at a given time" is a measurand. The component "protein" is sometimes termed "analyte"; **EXAMPLE 2:** The "amount-of-substance of glucose in plasma of a given person at a given time" is a measurand with the component "glucose."

measured quantity value – quantity value representing a measurement result[67]; **NOTE 1:** For a measurement involving replicate indications, each indication can be used to provide a corresponding measured quantity value. This set of individual measured quantity values can be used to calculate a resulting measured quantity value, such as an average or median, usually with a decreased associated measurement uncertainty[67]; **NOTE 2:** When the range of the true quantity values believed to represent the measurand is small compared with the measurement uncertainty, a measured quantity value can be considered to be an estimate of an essentially unique true quantity value and is often an average or median of individual measured quantity values obtained through replicate measurements[67]; **NOTE 3:** In the case where the range of the true quantity values believed to represent the measurand is not small compared with the measurement uncertainty, a measured value is often an estimate of an average or median of the set of true quantity values.[67]

measuring interval – set of values of quantities of the same kind that can be measured by a given measuring instrument or measuring system with specified instrumental measurement uncertainty, under defined conditions[67]; **NOTE 1:** The concentration range of results for which the test method functions to meet its intended use; **NOTE 2:** Measuring interval is determined by linearity, accuracy, and limit of detection.