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Proficiency Testing (External Quality Assessment) for Molecular Methods; Approved Guideline

This document provides guidelines for a quality proficiency testing program, including reliable databases; design control in the choice of materials and analytes; good manufacturing processes; documentation procedures; complaint handling; corrective and preventive action plans; and responsive timing of reports.

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

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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.

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- 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.

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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 the Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, PA 19087, USA.

VOLUNTEER PARTICIPATION

Healthcare 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.

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Abstract

As molecular methods become more commonly implemented, solid proficiency schemes are needed to further the development of this complex and rapidly growing area in laboratory medicine. Recognizing the essential role and responsibility of the organizations that provide these services, MM14-A—*Proficiency Testing (External Quality Assessment) for Molecular Methods; Approved Guideline* has been developed to guide them in best practices. It will also serve clinical laboratories with a benchmark for evaluation of new programs or, taken in principle, to guide their own program development when necessary. Specific sections discuss the design of materials; assignment of target result; distribution, receipt, and evaluation of data; and reporting responsibilities.

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Foreword

Medicine is science, experience, and art. While physicians, nurses, and other practitioners provide diagnosis, treatment, counseling, and patient management, their decisions and actions are based on scientific data as well as their knowledge, experience, and approach. Clinical laboratories provide a clear majority of the scientific data relied upon by practitioners; therefore, the integrity of the data is critical. This fact is intuitive among laboratory professionals and because of it, clinical laboratories have subscribed to blind-sample testing (proficiency testing) since the first programs in 1945, long before there were laws prescribing it. There is no other field of medicine that subjects itself to the rigor and detail of independent testing as the clinical laboratory. Proficiency testing has become one of the foundations of clinical laboratory work and as such, the organizations that administer these programs carry a great responsibility. Programs must be designed to indicate those laboratories and services that are not par with the standard of care without penalizing those that are. This also must be done in a manner that does not interfere with the main purpose of the clinical laboratory: to provide accurate, reliable clinical data to practitioners in a timely and cost-effective manner.

In this guideline, *Proficiency Testing (External Quality Assessment) for Molecular Methods; Approved Guideline*, we attempt to outline the basic principles and practices of quality proficiency testing organizations, specifically those serving the rapidly growing and complex area of molecular methods.

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 obstacles to harmonization. Despite these obstacles, CLSI recognizes that harmonization of terms facilitates the global application of standards and is an area that needs immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

In keeping with CLSI's commitment to align terminology with that of ISO, the following terms are used in MM14: *accuracy* is used in this document when referring to the closeness of the agreement between the result of a measurement and a true value of the measurand; and *trueness* is used when referring to the closeness of the agreement between the average value from a large series of measurements and to a true value of a measurand. The measurement of trueness is usually expressed in terms of *bias*. *Measurement procedure* has replaced *analytical method*; and *measuring range* has replaced *reportable range* when referring to a set of values of measurands for which the error of a measuring instrument is intended to lie within specified limits. The ISO terms *diagnostic sensitivity* and *diagnostic specificity* have replaced *clinical sensitivity* and *clinical specificity*. In Europe, for the most part, the term *clinical* is applied to the evaluation of medical products used on or in patients, or when referring to clinical studies of drugs, under much more stringent conditions.

Users of MM14-A should understand, however, that the fundamental meanings of the terms are similar and to facilitate understanding, terms are defined along with explanatory notes in the guideline's Definitions section.

Key Words

Molecular testing, performance testing, proficiency, quality assessment

Proficiency Testing (External Quality Assessment) for Molecular Methods; Approved Guideline

1 Scope

The purpose of this guideline is to complement currently available regulatory and guidance documents regarding the management and operations of proficiency testing programs. Presently, these documents guide the administration of such programs, but consideration of panel selection, analysis of data for evolving technologies, and reporting to responsible parties (i.e., other than government agencies) are not addressed. For molecular methods, these issues are important for all stakeholders, including regulatory agencies, accrediting agencies, proficiency test providers/organizations, proficiency test materials manufacturers, clinical laboratories, and test/reagent manufacturers. This document addresses the people who produce, distribute, and administer proficiency testing materials. It should enable clinical laboratories, manufacturers, and other organizations to develop and implement proficiency testing programs for nucleic acid testing.

This guideline does not address clinical laboratory inspection, accreditation, or other regulatory processes.

It is recognized that the term "molecular" encompasses a variety of molecules; however, this guideline focuses particularly on nucleic acid testing methods. Though written specifically to address needs in this area, the principles stated may be determined to be applicable to programs outside of nucleic acid testing.

Organizations and programs that send blinded samples to laboratories and analyze the submitted results carry several different names. Some of these are: proficiency testing, performance testing, quality assessment or assurance programs, quality control programs, and external quality assessment/assurance. Countries or regions may place regulatory distinctions on these names. To facilitate the readability of this document, the terms proficiency testing, proficiency testing provider/organization, proficiency test program, and PT have been chosen to describe such activities, and regulatory categorization is not implied unless specifically noted.

2 Introduction

"*There can be no more important task for the director of a clinical laboratory than to assess the precision and accuracy of the analytical procedures under his/her supervision. Maintenance of high standards of analysis not only serves as a scientific stimulus for the laboratory but is also of direct benefit to patients.*"[1]

Proficiency testing (PT)/external quality assessment (EQA) is a critical and integral part of clinical laboratory medicine. The reliability of information provided by the laboratory, a particular laboratory's reputation, and the commercial viability of a diagnostic test kit or an in-house developed method all are affected by these programs.

To adopt, implement, and maintain testing for specific analytes, clinical laboratories are regulated by rigorous law and practice standards. To develop, certify, manufacture, and distribute tests, manufacturers are regulated by laws that prescribe product development as well as the quality systems used by the organization.

Proficiency testing programs play a key role in the evaluation of clinical laboratories and manufactured tests. Laws, guidelines, and performance standards for these organizations are far less prescriptive than the entities they evaluate, adopted by inference in some cases, just beginning to develop in others, or unknown to the organizations that could use them. Because of this, a wide range of quality is represented

