



MM14-A2

Design of Molecular Proficiency Testing/ External Quality Assessment; Approved Guideline—Second Edition

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

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ISBN 1-56238-873-8 (Print)
ISBN 1-56238-874-6 (Electronic)
ISSN 1558-6502 (Print)
ISSN 2162-2914 (Electronic)

MM14-A2
Vol. 33 No. 5
Replaces MM14-A
Vol. 25 No. 24

Design of Molecular Proficiency Testing/External Quality Assessment; Approved Guideline—Second Edition

Volume 33 Number 5

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Abstract

As medical laboratory tests involving detection of nucleic acids become more common, well-designed and executed proficiency schemes are needed to assure quality and to further the development of this complex and rapidly growing area of laboratory medicine. MM14-A2—*Design of Molecular Proficiency Testing/External Quality Assessment; Approved Guideline—Second Edition* has been developed to guide the individuals and organizations responsible for providing proficiency testing (PT). It will also serve medical laboratories with a benchmark for evaluation of new programs or to facilitate development of laboratory-based PT or alternative assessment schemes when appropriate schemes are not available from formal programs. Specific sections discuss the design of PT programs; sources of materials; production, manufacture, and QA of samples; sample distribution; receipt and evaluation of data; and reporting responsibilities. Also discussed are examples of method-based PT programs and alternative assessment strategies and how they can be used to evaluate laboratory test performance. This document also lists and describes relevant regulatory and guidance documents related to PT.

Clinical and Laboratory Standards Institute (CLSI). *Design of Molecular Proficiency Testing/External Quality Assessment; Approved Guideline—Second Edition*. CLSI document MM14-A2 (ISBN 1-56238-873-8 [Print]; ISBN 1-56238-874-6 [Electronic]). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2013.

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Suggested Citation

CLSI. *Design of Molecular Proficiency Testing/External Quality Assessment; Approved Guideline—Second Edition*. CLSI document MM14-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.

Previous Editions:

September 2004, August 2005

Reaffirmed:

September 2018

ISBN 1-56238-873-8 (Print)
ISBN 1-56238-874-6 (Electronic)
ISSN 1558-6502 (Print)
ISSN 2162-2914 (Electronic)

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Foreword

This document replaces the first edition of the approved guideline, which was published in 2005. Several changes and additions were made in this edition; chief among them is the revision of the sections describing relevant regulatory and guidance documents and the addition of sections describing examples of method-based proficiency testing (PT) programs and alternative assessment strategies. This edition also recognizes and emphasizes the roles and responsibilities of the medical laboratory in providing PT through informal sample exchange programs.

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. Medical (clinical) laboratories provide a major source of information about the patient to the practitioners; therefore, the accuracy of the data and their interpretation is critical. This fact is intuitive among laboratory professionals. Medical laboratory directors organized blinded-sample testing and sample exchange studies long before the establishment of formal programs or laws and standards prescribing participation. Today, PT/external quality assessment (EQA) is an integral part of laboratory QA and, as such, the organizations that administer these programs carry a great responsibility. Programs should be designed to identify laboratory errors and recognize tests offered by medical laboratories that are not performing as expected. They also have an important role in educating laboratories about how their testing practices compare to those of other laboratories and ways in which they can improve the quality of their tests.

In this guideline, the basic principles and practices for PT/EQA organizations, as well as laboratories that provide PT/EQA through informal sample exchange programs, for molecular tests in the areas of human genetics, infectious disease, molecular oncology, and pharmacogenetics are outlined. In addition, practices such as method-based PT/EQA programs that can increase the scope of laboratory PT and provide valuable educational experiences are described. A section specifically addressing the medical laboratory as a provider of PT and PT materials for internal or external use is also included.

Key Words

Alternative assessment, EQA, external quality assessment, laboratory testing, manufacturers, molecular testing, proficiency testing, proficiency testing material, PT, PT materials, sample exchange

Design of Molecular Proficiency Testing/External Quality Assessment; Approved Guideline—Second Edition

1 Scope

The purpose of this guideline is to complement currently available regulatory and guidance documents regarding the management and operations of proficiency testing/external quality assessment (PT/EQA) programs. Presently, these documents guide the administration of such programs, but consideration of panel selection, analysis of data for evolving technologies and tests with many possible measurands, method-based PT/EQA, and reporting to participants are not addressed. For molecular methods, these issues are important for all stakeholders, including regulatory agencies, accrediting agencies, PT/EQA providers/organizations, PT/EQA materials manufacturers, medical (clinical) laboratories, and test/reagent manufacturers. This document addresses both large formal PT/EQA programs as well as medical laboratorians who produce, distribute, and administer PT/EQA schemes, and should provide guidance for the development and implementation of new PT/EQA programs for nucleic acid testing or modifying existing schemes.

This guideline does not address the process of testing and reporting PT/EQA in the medical laboratory, medical laboratory inspection, accreditation, or other regulatory processes.

This guideline focuses on nucleic acid (DNA and RNA) PT in the areas of human genetics, infectious disease, molecular oncology, and pharmacogenetics. Though written specifically to address needs in this area, the principles stated may 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. These challenge programs may be called PT/EQA, quality assessment or assurance programs, QC programs, ring trials, sample exchange, and EQA/assurance. Countries or regions may place regulatory distinctions on these names. To facilitate the readability of this document, the terms PT/EQA, PT/EQA provider/organization, and PT/EQA program have been chosen to describe such activities, and regulatory categorization is not implied unless specifically noted.

2 Introduction

PT/EQA is a critical and integral part of the medical laboratory QMS and is required by some accreditation bodies and regulations. All participants of a PT/EQA program receive identical or comparable samples to test for a particular measurand or set of measurands. These results are returned to the PT/EQA provider who analyzes and summarizes the data and provides feedback to the participants. Participation in PT/EQA allows laboratories to compare their analytical performance to that of other laboratories using similar or different methods. Participation in PT/EQA allows laboratories to identify analytical and interpretive errors, and may indicate internal problems with QC, calibration, assay design, or test interpretation. The ability to compare results obtained in different laboratories is especially important for molecular tests because the vast majority of them are developed by the laboratory offering the test (laboratory-developed test). The comparison afforded by participation in PT/EQA provides the laboratories and the accreditation bodies an assurance that the test, as developed by that laboratory, performs comparably to other available tests.

QA for molecular diagnostics is further complicated by the lack of established PT/EQA programs for most molecular genetic tests. This is due in part to the large number of tests available, the small number of laboratories that offer each test, the evolving technologies, and the complexity of the tests. In addition, it is often difficult to obtain suitable PT/EQA samples that represent the full range of measurands detected by the tests. This combination makes it economically and logistically difficult to offer formal PT/EQA

programs for every available test. In order to meet the requirement for PT/EQA, laboratories and some professional organizations often organize informal sample exchanges, and, hence, become PT/EQA providers. Method-based PT/EQA is being developed to address the logistical difficulty of providing a specific PT/EQA scheme for each molecular variation. This approach allows the broad evaluation of the ability of the laboratory to perform particular methods, such as DNA sequencing, DNA preparation, or quantitative PCR, and can provide QA to a large number of laboratories that perform these methods.

This document outlines the elements that should be addressed (as much as possible) by PT/EQA programs, both large formal programs and also the smaller, informal laboratory-based programs. It covers the design of PT/EQA programs, material sourcing and selection, sample production, and the transport, documentation, evaluation, and reporting of participant results. Approaches to evaluate molecular testing methods rather than individual tests are described. This document also provides a summary of regulatory and guidance documents relevant to PT/EQA, and is designed to complement ISO 17043,¹ which addresses general requirements for PT/EQA.

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 known infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. The Centers for Disease Control and Prevention (CDC) address this topic in published guidelines that focus on the daily operations of diagnostic medicine in human and animal medicine while encouraging a culture of safety in the laboratory.² For specific precautions for preventing the laboratory transmission of all known infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all known infectious diseases, refer to CLSI document M29.³

4 Terminology

4.1 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 for 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 and guidelines focuses on harmonization of terms to facilitate the global application of standards and guidelines.

In keeping with CLSI’s commitment to align terminology with established ISO standards, the following terms are used in MM14: *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. *Trueness* is used in this document 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; *measurement procedure* has replaced the term *analytical method* for a set of operations, used in the performance of particular measurements according to a given method; *measuring interval* 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 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 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:

Organization	Personnel	Process Management	Nonconforming Event Management
Customer Focus	Purchasing and Inventory	Documents and Records	Assessments
Facilities and Safety	Equipment	Information Management	Continual Improvement

MM14-A2 addresses the QSE 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.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
AUTO13	AUTO13	AUTO13	AUTO13	AUTO13	AUTO13	X AUTO13 EP32 GP27 GP29	AUTO13	AUTO13	AUTO13	GP27 GP29	GP27
QMS01	QMS01	QMS01	QMS01	QMS01	QMS01	MM01 MM05 MM06 QMS01	QMS01 QMS02	QMS01	QMS01	QMS01	QMS01

Path of Workflow

A path of workflow is the description of the necessary processes to deliver the particular product or service that the organization or entity provides. A laboratory path of workflow consists of the sequential processes: preexamination, examination, and postexamination and their respective sequential subprocesses. All laboratories follow these processes to deliver the laboratory’s services, namely quality laboratory information.

MM14-A2 does not address any of the clinical laboratory path of workflow steps. For a description of the 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
MM01	MM01	MM01	MM01	MM01	MM01	MM01	MM01	MM01
MM05			MM05	MM05	MM05	MM05	MM05	MM05
MM06	MM06	MM06	MM06	MM06	MM06	MM06	MM06	MM06
QMS01	QMS01	QMS01	QMS01	QMS01	QMS01	QMS01	QMS01	QMS01

Related CLSI Reference Materials*

- AUTO13-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.
- EP32-R** **Metrological Traceability and Its Implementation; A Report (2006).** This document provides guidance to manufacturers for establishing and reporting metrological traceability.
- GP27-A2** **Using Proficiency Testing to Improve the Clinical Laboratory; Approved Guideline—Second Edition (2007).** This guideline provides assistance to laboratories in using proficiency testing as a quality improvement tool.
- GP29-A2** **Assessment of Laboratory Tests When Proficiency Testing Is Not Available; Approved Guideline—Second Edition (2008).** This document offers methods to assess test performance when proficiency testing (PT) is not available; these methods include examples with statistical analyses. This document is intended for use by laboratory managers and testing personnel in traditional clinical laboratories as well as in point-of-care and bedside testing environments.
- 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.
- MM01-A3** **Molecular Methods for Clinical Genetics and Oncology Testing; Approved Guideline—Third Edition (2012).** This document provides guidance for the use of molecular biological techniques for detection of mutations associated with inherited medical disorders, somatic or acquired diseases with genetic associations, and pharmacogenetic response.
- MM05-A2** **Nucleic Acid Amplification Assays for Molecular Hematopathology; Approved Guideline—Second Edition (2012).** This guideline addresses the performance and application of assays for gene rearrangement and translocations by both polymerase chain reaction (PCR) and reverse-transcriptase PCR techniques, and includes information on specimen collection, sample preparation, test reporting, test validation, and quality assurance.
- MM06-A2** **Quantitative Molecular Methods for Infectious Diseases; Approved Guideline—Second Edition (2010).** This document provides guidance for the development and use of quantitative molecular methods, such as nucleic acid probes and nucleic acid amplification techniques of the target sequences specific to particular microorganisms. It also presents recommendations for quality assurance, proficiency testing, and interpretation of results.
- QMS01-A4** **Quality Management System: A Model for Laboratory Services; Approved Guideline—Fourth Edition (2011).** This document provides a model for medical laboratories that will assist with implementation and maintenance of an effective quality management system.
- QMS02-A6** **Quality Management System: Development and Management of Laboratory Documents; Approved Guideline—Sixth Edition (2013).** This document provides guidance on the processes needed for document management, including creating, controlling, changing, and retiring a laboratory's policy, process, procedure, and form documents in both paper and electronic environments.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

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PRINT ISBN 1-56238-873-8

ELECTRONIC ISBN 1-56238-874-6