



CLINICAL AND
LABORATORY
STANDARDS
INSTITUTE

3rd Edition

CLSI MM14™

Design of Molecular Proficiency Testing/ External Quality Assessment

CLSI MM14 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.

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

Clinical and Laboratory Standards Institute

Setting the standard for quality in medical laboratory testing around the world.

The Clinical and Laboratory Standards Institute (CLSI) is a not-for-profit membership organization that brings together the varied perspectives and expertise of the worldwide laboratory community for the advancement of a common cause: to foster excellence in laboratory medicine by developing and implementing medical laboratory standards and guidelines that help laboratories fulfill their responsibilities with efficiency, effectiveness, and global applicability.

Consensus Process

Consensus—the substantial agreement by materially affected, competent, and interested parties—is core to the development of all CLSI documents. It does not always connote unanimous agreement but does mean that the participants in the development of a consensus document have considered and resolved all relevant objections and accept the resulting agreement.

Commenting on Documents

CLSI documents undergo periodic evaluation and modification to keep pace with advances in technologies, procedures, methods, and protocols affecting the laboratory or health care.

CLSI's consensus process depends on experts who volunteer to serve as contributing authors and/or as participants in the reviewing and commenting process. At the end of each comment period, the committee that developed the document is obligated to review all comments, respond in writing to all substantive comments, and revise the draft document as appropriate.

Comments on published CLSI documents are equally essential and may be submitted by anyone, at any time, on any document. All comments are managed according to the consensus process by a committee of experts.

Appeal Process

When it is believed that an objection has not been adequately considered and responded to, the process for appeal, documented in the CLSI *Standards Development Policies and Processes*, is followed.

All comments and responses submitted on draft and published documents are retained on file at CLSI and are available upon request.

Get Involved—Volunteer!

Do you use CLSI documents in your workplace? Do you see room for improvement? Would you like to get involved in the revision process? Or maybe you see a need to develop a new document for an emerging technology? CLSI wants to hear from you. We are always looking for volunteers. By donating your time and talents to improve the standards that affect your own work, you will play an active role in improving public health across the globe.

For additional information on committee participation or to submit comments, contact CLSI.

Clinical and Laboratory Standards Institute

P: +1.610.688.0100

F: +1.610.688.0700

www.clsi.org

standard@clsi.org

Design of Molecular Proficiency Testing/External Quality Assessment

Lisa Kalman, PhD
Ann Moyer, MD, PhD

Simon Patton, PhD, Bsc(Hons)
Barbara Zehnbauer, PhD, FACB, FACMG

Abstract

As medical laboratory tests involving detection of nucleic acids become more common, well-designed and implemented proficiency schemes are needed to assure quality and to further the development of this complex and rapidly growing area of laboratory medicine. CLSI MM14—*Design of Molecular Proficiency Testing/External Quality Assessment* has been developed to guide the individuals and organizations responsible for providing proficiency testing (PT)/external quality assessment (EQA). It will also serve medical laboratories with a benchmark for evaluation of new programs or to facilitate development of laboratory-based PT/EQA or alternative assessment schemes when appropriate schemes are not available from formal programs. Specific subchapters discuss the design of PT/EQA 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/EQA programs and alternative assessment strategies and how they can be used to evaluate laboratory test performance. CLSI MM14 also lists and describes relevant regulatory and guidance documents related to PT/EQA.

CLSI. *Design of Molecular Proficiency Testing/External Quality Assessment*. 3rd ed. CLSI guideline MM14 (ISBN 978-1-68440-289-2 [Print]; ISBN 978-1-68440-290-8 [Electronic]). Clinical and Laboratory Standards Institute, USA, 2025.

The Clinical and Laboratory Standards Institute consensus process, which is the mechanism for moving a document through two or more levels of review by the health care community, is an ongoing process. Users should expect revised editions of any given document. Because rapid changes in technology may affect the procedures, methods, and protocols in a standard or guideline, users should replace outdated editions with the current editions of CLSI documents. Current editions are listed in the CLSI catalog and posted on our website at www.clsi.org.

If you or your organization is not a member and would like to become one, or to request a copy of the catalog, contact us at:

P: +1.610.688.0100 **F:** +1.610.688.0700 **E:** customerservice@clsi.org **W:** www.clsi.org



Copyright ©2025 Clinical and Laboratory Standards Institute. Except as stated below, any reproduction of content from a CLSI copyrighted standard, guideline, or other product or material requires express written consent from CLSI. All rights reserved. Interested parties may send permission requests to permissions@clsi.org.

CLSI hereby grants permission to each individual member or purchaser to make a single reproduction of this publication for use in its laboratory procedures manual at a single site. To request permission to use this publication in any other manner, e-mail permissions@clsi.org.

To read CLSI's full Copyright Policy, please visit our website at <https://clsi.org/terms-of-use/>.

Suggested Citation

CLSI. *Design of Molecular Proficiency Testing/External Quality Assessment*. 3rd ed. CLSI guideline MM14. Clinical and Laboratory Standards Institute; 2025.

Previous Editions:

September 2004, August 2005, May 2013

Reaffirmed:

September 2018

CLSI MM14-Ed3

ISBN 978-1-68440-289-2 (Print)

ISBN ~~978-1-68440-290-8~~ (Electronic)

ISSN 1558-6502 (Print)

ISSN 2162-2914 (Electronic)

Volume 45, Number 9

.....

Committee Membership

Consensus Council

The Consensus Council sets priorities for CLSI standards development and votes on Final Draft documents to confirm that process requirements have been met. Consensus Council members are listed on the CLSI website: <https://clsi.org/standards-development/consensus-council/>

Expert Panel on Molecular Diagnostics

Expert panel volunteers support the development of CLSI documents by providing technical expertise in specialty areas. Expert panel members are listed by area of expertise on the CLSI website: <https://clsi.org/standards-development/expert-panels/>

Acknowledgment

CLSI, the Consensus Council, and the Expert Panel on Molecular Diagnostics gratefully acknowledge the following volunteers for their important contribution to the limited revision of CLSI MM14:

Lisa Kalman, PhD
Centers for Disease Control
and Prevention
USA

Simon Patton, PhD, Bsc(Hons)
European Molecular Genetics Quality
Network
United Kingdom

Barbara Zehnbauer, PhD, FACB, FACMG
Emory University Hospital
USA

Ann Moyer, MD, PhD
Mayo Clinic
USA

Contents

Abstract	i
Committee Membership	iii
Foreword	vii
Chapter 1: Introduction	1
1.1 Scope	2
1.2 Standard Precautions	2
1.3 Terminology	3
Chapter 2: Overview	9
Chapter 3: Survey of Regulatory and Guidance Documents Regarding Proficiency Testing	11
Chapter 4: Design	13
4.1 Regulatory Considerations	15
4.2 Sample Composition	16
4.3 Number and Variety of Test Samples	18
4.4 Interpretation	20
4.5 Process Checklist	21
4.6 Handling Complaints and Inquiries	21
Chapter 5: Material Sourcing/Collection	23
5.1 Laws and Guidelines Governing Human Specimen Acquisition	24
5.2 Confidentiality and Privacy	24
5.3 Sample Sourcing	25
Chapter 6: Production/Manufacture	29
6.1 Sample Preservation	30
6.2 Production	31
6.3 Characterization	32
6.4 Proficiency Testing Material Stability	32
6.5 Sample Retention	33
Chapter 7: Transportation of Samples for Proficiency Testing Programs	35
7.1 Specimen Types	36
7.2 Packaging and Transport	37
7.3 Sample Rejection Criteria	38

Content (Continued)

Chapter 8: Documentation to Exchange Information	39
8.1 Documentation Requirements	40
8.2 General Information About the Proficiency Testing/External Quality Assessment Scheme	40
8.3 Registration and Confirmation	40
8.4 Preparation and Transport of Samples	41
8.5 Result Form	42
8.6 Reporting of Results to Participants	43
Chapter 9: Provider Results Review and Evaluation	47
9.1 Issues to Be Considered	48
9.2 Defining the “Correct” Result	48
9.3 Published Evaluations of Proficiency Testing/External Quality Assessment Provider Results	50
Chapter 10: Complementary and Supplementary Approaches to Proficiency Testing/External Quality Assessment Programs	51
10.1 Laboratories Acting as Proficiency Testing Providers	52
10.2 Alternative Proficiency Testing/External Quality Assessment Strategies	52
Chapter 11: Supplemental Information	57
References	58
Appendix A. Globally Influential Documents Addressing Proficiency Testing: Relevance to and Effect on Stakeholders	70
Appendix B. Process Checklist Example	75
Appendix C. Useful Websites for Information on Shipping Proficiency Testing/External Quality Assessment Samples	76
Appendix D. Example Registration Form for Proficiency Testing/External Quality Assessment Challenge/Scheme	77
Appendix E. Example Instructions Manual	80
Appendix F. Example of Clinical Information Related to the Proficiency Testing/External Quality Assessment Sample	82
Appendix G. Example Sections From a Proficiency Testing/External Quality Assessment Result Reporting Form	83
Appendix H. Example Confidentiality Form	86
Appendix I. Example Data From a Participant Summary Report	87
The Quality Management System Approach	94

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. 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/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 CLSI MM14, 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 diseases, molecular oncology, and pharmacogenetics are outlined. In addition, practices such as method-based PT/EQA programs that can increase the scope of laboratory PT/EQA and provide valuable educational experiences are described. A subchapter specifically addressing the medical laboratory as a provider of PT/EQA and PT/EQA materials for internal or external use is also included.

Overview of Changes

CLSI MM14-Ed3 was revised in 2025 under the Limited Revision Process and replaces CLSI MM14-A2, which was published in 2013. Several changes were made in this edition, including:

- Improving the terminology to also accommodate CLSI's recommendation for harmonization of terms
- Including additional types of reference samples, such as *in silico* modified nucleic acid sequence data files, clustered regularly interspaced short palindromic repeat–engineered cell lines, cell-free tumor DNA, and formalin-fixed, paraffin-embedded tissue sections or cores
- Including additional sources of reference samples from commercial and other sources
- Discussing different formats for PT and EQA

NOTE: The content of CLSI MM14 is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

KEY WORDS

alternative assessment

manufacturers

proficiency testing material

external quality assessment

molecular testing

sample exchange

laboratory testing

proficiency testing

Chapter ①

Introduction

Design of Molecular Proficiency Testing/External Quality Assessment

1 Introduction

1.1 Scope

The purpose of CLSI MM14 is to complement currently available regulatory and guidance documents regarding the management and operations of proficiency testing (PT)/external quality assessment (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. CLSI MM14 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.

CLSI MM14 does not address the process of testing and reporting PT/EQA in the medical laboratory, medical laboratory inspection, accreditation, or other regulatory processes.

CLSI MM14 focuses on nucleic acid (DNA and RNA) PT/EQA in the areas of human genetics, infectious diseases, molecular oncology, and pharmacogenetics. Although 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 CLSI MM14, 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.

1.2 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 known infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. Published guidelines are available that discuss the daily operations of diagnostic medicine in humans and animals while encouraging a culture of safety in the laboratory.¹ 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 M29.²