CLINICAL AND LABORATORY STANDARDS INSTITUTE®

3rd Edition

CLSI MM06™

Quantitative Molecular Methods for Infectious Diseases

CLSI MM06 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.

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

CLSI MM06-Ed3
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Replaces CLSI MM06-Ed2

Quantitative Molecular Methods for Infectious Diseases

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Abstract

CLSI MM06—*Quantitative Molecular Methods for Infectious Diseases* recognizes the increased use of quantitative molecular methods for measuring and monitoring the concentration of pathogens in patient specimens. CLSI MM06 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, and presents recommendations for quality assurance, proficiency testing, and interpretation of results.

Issues specific to the quantification of nucleic acid in diagnostic testing and monitoring, particularly in viral diseases, include an update on technologies used in molecular quantification; specimen handling and preparation; standards, calibrators, and reference materials; analytical and clinical verification/validation; reporting and interpreting results; clinical utility; and recommendations for manufacturers and clinical laboratories.

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Foreword

Quantification of pathogens has become the standard of care for the initial diagnosis and continued monitoring of multiple infections that are predominantly of viral origin. The measurement of viral load has proven prognostic utility in patients infected with several pathogenic viruses, and the clinical utility of others is an area of active investigation. Quantitative tests for the measurement of some of these pathogens have become fully automated, and viral load testing is now performed routinely in a significant number of clinical laboratories.

The first edition of CLSI MM06 established the original guidelines for laboratory tests that quantified viruses for diagnosis and monitoring of infected patients. CLSI MM06 is intended for use with CLSI MM03[1] and specifically addresses the changes in technology, performance, assay verification, interpretation, and QC for quantitative molecular methods in the diagnosis and monitoring of infectious diseases.

Overview of Changes

CLSI MM06-Ed3 replaces CLSI MM06-Ed2, published in 2010. Several changes were made to this edition, including:

- Updating Chapter 3 to bring awareness to newer applications, including vector monitoring during gene therapy and drug resistance mutations using next-generation sequencing.
- Updating all chapters for procedural, technological, and regulatory aspects that specifically cover considerations when developing quantitative molecular methods for infectious diseases.
- Updating important aspects of matrix selection, technology selection, verification and validation, and quality assurance unique to quantitative molecular-based testing to include the latest guidelines and best practices.

NOTE: The content of CLSI MM06 is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

KEY WORDS

dynamic range
infectious diseases
limit of detection
limit of quantification
nucleic acid
quantification
standards
viral load

Chapter 1

Introduction

Quantitative Molecular Methods for Infectious Diseases

1 Introduction

1.1 Scope

CLSI MM06 is to be used for the implementation of tests for diagnostic purposes after the benefits and potential risks associated with the use of the test in clinical practice have been considered. Specimen handling and preparation; standards, calibrators, and reference materials; analytical and clinical verification/validation; reporting and interpreting results; and QC and clinical utility are the focus of CLSI MM06. CLSI MM06 does not establish a clinically acceptable limit of quantification (LoQ) because consensus for most assays is currently lacking on this issue.

CLSI MM06 is intended for manufacturers or laboratories that develop tests, laboratories that perform or intend to implement such tests, clinicians that use the results to diagnose or manage patients, and agencies that regulate their use.

Nucleic acid testing for infectious agents poses unique issues; quantification introduces additional complexity. With the advent of commercially available quantitative kits and the increase in quantitative laboratory-developed testing, a guideline for the development, verification, validation, implementation, and quality assurance of these assays is warranted. At the time of the development of CLSI MM06, clinical use of quantitative molecular assays was primarily applicable to viral diseases. CLSI MM06 applies to assays used to identify clinical disease and monitor disease progression and prognosis, therapeutic efficacy, and the emergence of active disease in chronic viral infections or during reactivation. In principle, the methodologies can also be applied to other infectious agents and disease processes.

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 bloodborne 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.[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 M29.[3]

1.3 Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization whenever 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 different countries and regions and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. CLSI recognizes its important role in these efforts, and its consensus process focuses on harmonization of terms to facilitate the global application of standards and guidelines. Table 1 is provided to clarify the intended interpretations of the following terms.

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