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CLINICAL AND LABORATORY STANDARDS INSTITUTE®

August 2008

M50-A

Quality Control for Commercial Microbial Identification Systems; Approved Guideline

NOTE: CLSI document M50-A no longer applies to US laboratories subject to the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The streamlined QC guidance provided in this document does not replace the need for an individualized quality control plan (IQCP), effective as of 1 January 2016. IQCP resources are available, and links can be found on the CLSI website (www.clsi.org). M50-A might be applicable to international laboratories.

This document provides guidance for quality control of commercial systems for microbial identification from culture, including information that pertains to manufacturers, distributors, and laboratory users. The intent is to ensure optimal performance of a microbial identification system in an efficient (streamlined) manner.

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

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Quality Control for Commercial Microbial Identification Systems; Approved Guideline

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Abstract

Clinical and Laboratory Standards Institute document M50-A—*Quality Control for Commercial Microbial Identification Systems; Approved Guideline* includes a process for streamlined quality control (QC) of commercial microbial identification systems (MISs) that utilize multiple substrates and/or reagents to identify aerobic or anaerobic bacteria, yeasts, moulds, or yeast-like algae from culture. It specifies responsibilities of the manufacturer, distributor, and user. M50-A includes guidelines that may be followed when using an MIS of proven reliability to take a modified QC approach, rather than meeting requirements included in the Clinical Laboratory Improvement Amendments of 1988 regulations. The streamlined QC approach was developed following an evaluation of data provided by the American Society for Microbiology for a survey conducted to determine the QC failure rates of commercial MISs. The data showed a failure rate of less than 0.1% for all commercial MISs surveyed. This document is based on United States (US) regulations and will also serve as a useful resource for a wider audience. It is anticipated that M50-A will be used extensively in the United States and internationally to reduce resources spent on excessive QC testing.

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Contents

Foreword

This document is based on United States (US) regulations and will also serve as a useful resource for a wider audience. It is anticipated that M50-A will be used extensively in the United States and internationally to reduce resources spent on excessive quality control (QC) testing.

Historically, in the United States, the accepted practice for QC of conventional biochemical reagents or miniaturized systems used for microbial identification from culture involved checking positive and negative reactivity with each batch, lot number, and shipment of reagents or systems. This practice was codified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) for any commercial microbial identification system (MIS) using two or more substrates, two or more reagents, or a combination of both.[1] The CLIA regulations require each laboratory to test every substrate and/or reagent that is part of an MIS for positive and negative reactivity, using biologic QC organisms, with each batch, lot number, and shipment. Over time, as MISs have evolved and become more complex, they have incorporated increasing numbers of reagents and substrates; this has resulted in the need for an increased number of QC organisms to check positive and negative reactivity for all components. In addition, some MISs now utilize identification algorithms that do not allow for total compliance with this CLIA QC requirement, but have proven reliability in organism identification. Thus, in some cases, meeting this QC requirement is now impossible; whereas in other cases, it imposes financial and workflow burdens on microbiology laboratories, and may be unnecessary for MISs of proven reliability produced by manufacturers that meet quality standards and applicable regulations for control and distribution.

After considering this issue, in 2005, the American Society for Microbiology (ASM), at the suggestion of the Clinical Laboratory Improvement Advisory Committee (CLIAC), conducted a microbiology laboratory survey to determine the QC failure rates of commercial MISs in a random selection of laboratories that perform bacterial and fungal identification from culture. Two hundred ninety-two laboratories provided valid responses to the survey for 9886 lots of MISs. The laboratories varied in the type of facility, source of primary accreditation, and number of cultures performed per year. The number of different MISs used in the responding laboratories to identify gram-positive and gram-negative aerobic bacteria, *Neisseria/Haemophilus*, anaerobic bacteria, and yeasts ranged from 1 to 13, with the majority of laboratories using five or more systems. Of the 9886 lots of MISs tested, 912 lots failed QC. For these failures, 905 were caused by the QC organism(s) used; and in seven cases, the failure was due to the MIS itself, specifically certain reagents and/or substrates that appeared to be labile and did not react as expected. In these cases, the faulty MIS lots were replaced by the manufacturer. Based on these seven instances, the failure rate due to the MIS was less than 0.1% for all MISs tested.[2]

ASM presented these QC survey data to CLIAC, and recommended that the Clinical and Laboratory Standards Institute (CLSI) use its consensus process to analyze the data and develop guidelines to address appropriate QC for MISs.[3] Subsequently, CLSI recommended convening a subcommittee representing laboratorians, manufacturers, and government (specifically, the Centers for Disease Control and Prevention [CDC], Centers for Medicare & Medicaid Services [CMS], and US Food and Drug Administration [FDA]) to determine whether and under what circumstances streamlined QC for MIS would be acceptable. This consensus document describes the acceptable criteria for allowing streamlined QC, as compared to the requirements specified by the CLIA regulations for MISs produced by manufacturers that meet specific quality standards and regulations. It is intended to provide practical guidelines for laboratories to ensure the quality of their microbial identification results when using commercial MISs. It is anticipated that these guidelines will receive widespread use in the United States and internationally, and could reduce unnecessary costs and other resources spent on excessive QC testing.

Key Words

Commercial microbial identification system (MIS), key indicator strain, quality control (QC), reagent, streamlined QC, substrate

Quality Control for Commercial Microbial Identification Systems; Approved Guideline

1 Scope

This document provides quality control (QC) information for commercially available microbial identification systems (MISs), which are test systems that utilize multiple substrates and/or reagents to identify aerobic or anaerobic bacteria, yeasts, moulds, or yeast-like algae (eg, *Prototheca* species) grown from culture. It does not address primary isolation media, chromogenic agars, direct antigen tests, stains, or molecular methodologies used for microbial identification; nor does it address QC of antimicrobial susceptibility tests. The document specifies the QC responsibilities of the manufacturer, distributor, and user, and identifies conditions under which an MIS with proven reliability can qualify for streamlined QC testing. The modified approach may be applied after the user verifies acceptable MIS performance as specified in this guideline. Implementation of streamlined QC testing by users assumes that the MIS performance is monitored by overall quality assurance (QA) programs on the part of the manufacturer, distributor, and user.

This document is based on United States (US) regulations and will also serve as a useful resource for a wider audience. It is anticipated that M50-A will be used extensively in the United States and internationally to reduce resources spent on excessive QC testing.

2 Introduction

Prior to 1998, the US Food and Drug Administration (FDA) considered MISs used clinically as Class I nonexempt medical devices that required premarket notification (510[k]) submission and review. Under the FDA Modernization Act of 1997, this type of medical device was reclassified to Class I exempt status and no longer requires 510(k) clearance.[4] Today, MISs that are marketed for clinical use in the United States should be registered and the devices listed with the FDA. In meeting the FDA Quality System Regulation (QSR) for Current Good Manufacturing Practice requirements, the same criteria as prior to reclassification must be met by manufacturers to support the intended use, and to establish performance characteristics for a device just as though a 510(k) submission was required.[5] The data package must be assembled and retained through the life of the product at the manufacturer's site, and must be available for inspection by the FDA. If an MIS or other clinical product is marketed globally, other regulatory agencies may require submission of a data package and/or registration of the product prior to marketing (eg, *In Vitro* Diagnostic Directive 98/79/European Commission in the European Union, Ministry of Health in Japan).

In the United States and its territories, any testing of human specimens for diagnosis, prevention, or treatment of disease or assessment of health is subject to the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) regulations.[6] Also subject to CLIA are facilities outside the United States or its territories that perform testing as described above when such tests are referred by, and the results are returned to, a facility or authorized person in the United States or its territories. As per the CLIA regulations effective 1 September 1992, prior to performing patient testing using a commercial MIS, each laboratory needs to verify that it can obtain performance specifications comparable to those of the manufacturer.[7] For a commercial MIS in use before this date, no verification studies are required. Regardless of the implementation date in a laboratory, for QC of a commercial MIS, the CLIA regulations require a laboratory to check every reagent and/or substrate of each batch, lot number, and shipment when prepared or opened for positive and negative reactivity (42 CFR [Code of Federal Regulations] 493.1256 [e][1]).[1] The CLIA interpretive guidelines (42 CFR 493.1261[a]) also state that the laboratory must use control organisms to verify positive and negative reactivity.[8] This ongoing QC testing is a means of

validating that the MIS continues to perform acceptably throughout its use, as was demonstrated by the laboratory in the initial verification study.

To meet the CLIA regulations for an MIS, in many cases, laboratories need to perform extensive QC testing, even though the perceived value of this testing is low considering the frequency of product failures. The variable reactivity of some QC organisms can also lead to retesting that is considered of questionable value. The 2005 American Society for Microbiology (ASM) survey conducted to determine QC failure rates and the value of such extensive testing and retesting showed that real product failure was extremely rare (7/9886 or <0.1%), in comparison to failure associated with QC organism variability that was resolved after retesting (905/9886 or 9.2%).[3] However, on review of the QC data with a variety of individual test systems, predictable patterns of failure due to a specific substrate were noted for some systems. As one example, xylose was found to be reactive when it should have been nonreactive with one particular MIS. Thus, while testing every substrate for a positive and negative reaction may not be necessary to identify the test system failure, evaluating the reaction of specific substrates for a given MIS may be appropriate in a scheme for streamlined QC. In this example, because pentose sugars such as xylose may be heat-labile, the streamlined QC recommended by the manufacturer should include checking the stability of this carbohydrate. Data from the ASM survey suggest that before a streamlined QC scheme is adopted by a laboratory, the manufacturer needs to recommend a scheme that includes checking appropriate organisms (ie, key indicator strains) to assess the performance of the MIS and detect degradation of labile reagents and/or substrates. Not all manufacturers may choose to provide this information for their MISs. If not, the laboratories using those systems must meet the comprehensive CLIA QC requirements.

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 infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the US Centers for Disease Control and Prevention.[9] For specific precautions for preventing the laboratory transmission of all infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious disease, refer to CLSI document M29.[10]

4 Terminology

4.1 Definitions

accuracy – the ability of an MIS to correctly identify the organism being tested.

automated MIS – MIS in which all, or most, steps (eg, inoculation, incubation, result interpretation) are performed by an instrument.

batch – all tubes, plates, or containers of an MIS that have the same lot number and are received in a single shipment.

Certificate of Analysis (COA) – document provided by the manufacturer stating that the released product meets all Quality System Regulation (QSR) requirements and quality control specifications; **NOTE:** COAs apply to individual lots of the product (ie, lot-specific).

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 approach is based on the model presented in the most current edition of CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care.* 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:

Documents & Records	Equipment	Information Management	Process Improvement
Organization	Purchasing & Inventory	Occurrence Management	Customer Service
Personnel	Process Control	Assessments—External & Internal	Facilities & Safety

M50-A addresses the QSEs 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.

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessments—External & Internal	Process Improvement	Customer Service	Facilities & Safety
M07		GP21			X EP12 M02 M07 M22 M29 MM06			MM06			M29

Adapted from CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*.

Path of Workflow

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, CLSI/NCCLS document GP26—*Application of a Quality Management System Model for Laboratory Services* defines a clinical laboratory path of workflow, which consists of three sequential processes: preexamination, examination, and postexamination. All clinical laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

M50-A addresses the clinical laboratory path of workflow steps 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.

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
MM06	MM06	MM06	MM06	MM06	X M02 M07 M100 MM06	X M02 M07 M100 MM06	X M02 M07 M100 MM06	

Adapted from CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*.

Related CLSI Reference Materials*

EP12-A2 **User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline—Second Edition (2008).** This document provides a consistent approach for protocol design and data analysis when evaluating qualitative diagnostic tests. Guidance is provided for both precision and method-comparison studies.

GP21-A2 **Training and Competence Assessment; Approved Guideline—Second Edition (2004).** This document provides background information and recommended processes for the development of training and competence assessment programs that meet quality/regulatory objectives.

M02-A9 **Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard—Ninth Edition (2006).** This document contains the current CLSI-recommended methods for disk susceptibility testing, criteria for quality control testing, and updated tables for interpretive zone diameters.

M07-A7 **Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Seventh Edition (2006).** This document addresses reference methods for the determination of minimal inhibitory concentrations (MICs) of aerobic bacteria by broth macrodilution, broth microdilution, and agar dilution.

M22-A3 **Quality Control for Commercially Prepared Microbiological Culture Media; Approved Standard—Third Edition (2004).** This document contains quality assurance procedures for manufacturers and users of prepared, ready-to-use microbiological culture media.

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.

M100-S18 **Performance Standards for Antimicrobial Susceptibility Testing; Eighteenth Informational Supplement (2008).** This document provides updated tables for the Clinical and Laboratory Standards Institute (CLSI) antimicrobial susceptibility testing standards M02-A9 and M07-A7.

MM06-A **Quantitative Molecular Methods for Infectious Diseases; Approved Guideline (2003).** 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.

* Proposed-level documents are being advanced through the Clinical and Laboratory Standards Institute consensus process; therefore, readers should refer to the most current editions.

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