

# Quality Control for Commercial Microbial Identification Systems; Proposed Guideline

*PLEASE*



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Please send your comments on scope, approach, and technical and editorial content to CLSI.

Comment period ends

10 March 2008

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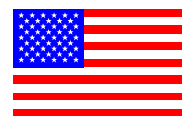
*COMMENT*

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 national application developed through the Clinical and Laboratory Standards Institute consensus process.



(Formerly NCCLS)



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*Advancing Quality in Health Care Testing*

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## VOLUNTEER PARTICIPATION

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## Quality Control for Commercial Microbial Identification Systems; Proposed Guideline

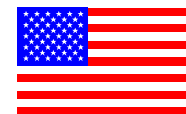
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### Abstract

Clinical and Laboratory Standards Institute document M50-P—*Quality Control for Commercial Microbial Identification Systems; Proposed 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-P 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. While this document will serve as a useful resource for a wider audience, it is based on US regulations. It is anticipated that M50-P will be used extensively in the United States and internationally to reduce resources spent on excessive QC testing.

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## Foreword

Historically, in the United States, the accepted practice for quality control (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.<sup>1</sup> 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 of MIS. 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. Meeting this QC requirement 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.

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.<sup>2</sup> 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.

### Invitation for Participation in the Consensus Process

An important aspect of the development of this and all CLSI documents should be emphasized, and that is the consensus process. Within the context and operation of CLSI, the term “consensus” means more than agreement. In the context of document development, “consensus” is a process by which CLSI, its members, and interested parties (1) have the opportunity to review and to comment on any CLSI publication; and (2) are assured that their comments will be given serious, competent consideration. Any CLSI document will evolve as will technology affecting laboratory or health care procedures, methods, and protocols; and therefore, is expected to undergo cycles of evaluation and modification.

The Area Committee on Microbiology has attempted to engage the broadest possible worldwide representation in committee deliberations. Consequently, it is reasonable to expect that issues remain unresolved at the time of publication at the proposed level. The review and comment process is the mechanism for resolving such issues.

The CLSI voluntary consensus process is dependent upon the expertise of worldwide reviewers whose comments add value to the effort. At the end of a 60-day comment period, each subcommittee is obligated to review all comments and to respond in writing to all which are substantive. Where appropriate, modifications will be made to the document, and all comments along with the subcommittee's responses will be included as an appendix to the document when it is published at the next consensus level.

**Key Words**

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

## Quality Control for Commercial Microbial Identification Systems; Proposed 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 QC performance as specified in this guideline. Implementation of streamlined QC testing by users assumes that the MIS performance is monitored by overall quality assurance programs on the part of the manufacturer, distributor, and user.

### 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.<sup>3</sup> 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 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.<sup>4</sup> The data package that is submitted 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.<sup>5</sup> 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.<sup>6</sup> 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 493.1256 [e][1]).<sup>1</sup> The CLIA interpretive guidelines (42 CFR 493.1261[a]) also state that the laboratory must use control organisms to verify positive and negative reactivity.<sup>7</sup>

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 ASM survey conducted to determine QC failure rates and the value of such