Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters; Approved Guideline—Third Edition

This document addresses the required and recommended data needed for the selection of appropriate interpretive criteria and quality control ranges for antimicrobial agents. A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.
Clinical and Laboratory Standards Institute

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Guideline A document developed through the consensus process describing criteria for a general operating practice, procedure, or material for voluntary use. A guideline may be used as written or modified by the user to fit specific needs.

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- the revision of documents in response to comments by users
- the acceptance of a document as a consensus standard or guideline.

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VOLUNTEER PARTICIPATION

Health care professionals in all specialties are urged to volunteer for participation in CLSI projects. Please contact us at customerservice@clsi.org or +610.688.0100 for additional information on committee participation.
Abstract

Clinical and Laboratory Standards Institute document M23-A3—Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters; Approved Guideline—Third Edition offers guidance for developing interpretive criteria and quality control ranges for antimicrobial susceptibility tests against aerobic and anaerobic bacteria, and yeasts performed by CLSI antimicrobial susceptibility testing standards. It describes the data utilized by the Antimicrobial Susceptibility Testing and Antifungal subcommittees to establish these interpretive criteria and QC ranges for antimicrobial agents, including MIC distributions against relevant microorganisms, pharmacokinetic (PK) and pharmacodynamic (PD) characteristics, and clinical outcome data. As antimicrobial agents are used in practice, additional experience accrued may be used to reassess interpretive criteria or QC ranges. Users of these guidelines should understand that susceptibility test results cannot predict with absolute certainty clinical outcomes. They should be used along with the best clinical judgment and laboratory support to draw the best conclusions serving the patient.

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Contents

Abstract ................................................................. i

Committee Membership ........................................................ iii

Foreword ................................................................. ix

Subcommittee on Antimicrobial Susceptibility Testing Mission Statement ....................... xi

1 Scope ........................................................................ 1
   1.1 Guidelines for Antifungal Agents .............................. 1

2 Introduction .................................................................. 1

3 Terminology .................................................................. 2
   3.1 Definitions .......................................................... 2
   3.2 Abbreviations/Acronyms ........................................ 3

4 Subcommittee Requirements for Initial Assessment or Reassessment of Interpretive
   Criteria or Quality Control Ranges ................................. 4
   4.1 Time Sequence for Presentation Relating to New Antimicrobial Agents ................ 4
   4.2 Reassessment of Previously Established Interpretive Criteria or Quality Control
       Ranges ................................................................. 7
   4.3 Presentation .......................................................... 7

5 Determining Susceptibility Test Interpretive Criteria ...................................................... 7
   5.1 Overview of the Process ........................................... 7
   5.2 Data for Determining Interpretive Criteria ..................... 8

6 Reassessment of Interpretive Criteria ............................................................................. 15
   6.1 Situations in Which Reassessment of Interpretive Criteria May Be Considered ....... 16
   6.2 Guidelines for Data Presentation and Procedures for Reassessment of Interpretive
       Criteria ................................................................. 18
   6.3 Data to Be Examined in the Reassessment of Interpretive Criteria ......................... 20

7 Dilution Test Methods (CLSI documents M07, M11, M26) .............................................. 21
   7.1 Validation of Microbiologic Data Derived From Other Than Reference Methods ....... 22
   7.2 Use of Microbiological Data Derived From Previously Accepted Reference
       Methods ............................................................... 23

8 Disk Diffusion Test Methods (CLSI document M02) ......................................................... 23
   8.1 Disk Content Studies ............................................... 23
   8.2 Evaluation of Disk Diffusion Susceptibility Tests ............................................... 24

9 *Cross-Resistance and Cross-Susceptibility Studies ......................................................... 27

10 Quality Control Ranges .............................................................................................. 27
    10.1 *Preliminary Quality Control Testing (Tier 1) ....................................................... 27
    10.2 *Requirements for Establishing Acceptable Quality Control Ranges (Tier 2 QC
        Study) .......................................................................... 29
    10.3 Confirmation and Reassessment of Quality Control Ranges (Tier 3 QC
        Monitoring or Supplemental Studies) ............................................. 32
Contents (Continued)

11 Resolving Differences Between CLSI, Regulatory Agencies, and Other Interpretive
Criteria-Setting Organizations ................................................................. 34

References............................................................................................................. 36

Appendix A. Suggested Information to Be Contained on Package Cover Page (see note) .......... 37

Appendix B. Drug “X” Minimal Inhibitory Concentration vs Zone Diameter (495 challenge
organisms) ........................................................................................................ 38

Appendix C. Sample Data Presentations ............................................................ 40

Summary of Consensus Comments and Subcommittee Responses ......................... 41

Summary of Delegate Comments and Working Group Responses ............................. 42

The Quality Management System Approach ....................................................... 44

Related CLSI Reference Materials ....................................................................... 45
Foreword

CLSI is responsible for the development of standardized reference methods for *in vitro* tests that measure the susceptibility of bacteria to antimicrobial agents. In this regard, the CLSI Subcommittee on Antimicrobial Susceptibility Testing is responsible for developing and updating the following susceptibility testing standards:

M02—*Performance Standards for Antimicrobial Disk Susceptibility Tests*;¹

M07—*Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*;²

M11—*Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria*; and³

M100—*Performance Standards for Antimicrobial Susceptibility Testing*;⁴

In addition, the subcommittee developed a new guideline, CLSI document M45-A—*Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria*⁵ to assist laboratories in testing organisms for which no susceptibility testing standards currently exist.

M23-A3 describes information required for review by the subcommittee when determining interpretive criteria and quality control (QC) ranges for inclusion in the above noted documents. M23 provides guidance applicable both to new antimicrobial agents about to be introduced into clinical use, and to antimicrobial agents already marketed, but requiring subsequent reassessment as new information becomes available.

All sections of the guideline preceded by an asterisk (*) describe information required for review by the subcommittee. All other sections describe additional information useful to the subcommittee in supporting the selection of interpretive criteria and QC ranges, and achieving the objectives of M23.

The previous edition of this document (M23-A2)⁶ updated and described with great clarity the process required to establish quality control ranges, and to evaluate acceptable discrepancy rates between susceptibility test results obtained using dilution and disk diffusion methods. The document provided formal guidance on the use of pharmacodynamic analysis in the development of interpretive criteria and a more complete description of clinical outcomes data needed to support proposed breakpoints. M23-A2 also conveyed that reassessment of previously assigned breakpoints or QC parameters might be required, and emphasized the need to consider the potential impact of such changes on similar products to minimize the possibility of creating unfair advantages or disadvantages for one antimicrobial agent relative to another. In addition, the previous edition addressed the source of occasional discrepancies between breakpoints determined by CLSI and regulatory agencies, and pointed out that every effort should be made to resolve such differences.

In updating the M23 document, the working group was cognizant of the unique position of CLSI in providing guidance to microbiology laboratories globally, enabling them to develop the most accurate susceptibility test results to assist clinicians who treat patients. CLSI can respond quickly to emerging mechanisms of antimicrobial resistance, provide assistance for testing unusual or infrequently isolated pathogens, and address changing antimicrobial agent usage patterns and potential public health threats. Through a process of continuous reevaluation of surveillance data and the scientific basis of antimicrobial action, and through active dialogue with microbiologists who employ these tests daily in “real world” situations, CLSI can dynamically reassess, modify, and improve standards to provide the most relevant, cost-effective, and reliable results for the benefit of patients across the globe.
Foreword (Continued)

One great strength of CLSI is decisions are made in an open forum, where representatives of industry, government agencies, and the professions can present diverse opinions that are debated among all stakeholders according to CLSI’s consensus process. International participants bring the broadest possible perspective into this consensus process. However, the working group was cognizant of the fact that the very transparency of these discussions, which often reflect evolving concepts and novel tools relevant to this process, can sometimes give the appearance of inconsistency or unpredictability. Therefore, a major goal of this document update was to define more clearly how information is used by the subcommittee to develop standards and to offer greater guidance to sponsors preparing for presentations to the subcommittee.

The M23 guideline is a key foundation document for CLSI’s widely used “family” of susceptibility testing documents. The purpose of M23 is to offer direction and guidance for developing relevant scientific data used by the Subcommittee on Antimicrobial Susceptibility Testing to establish interpretive criteria and quality control ranges for CLSI’s antimicrobial susceptibility testing standards. The intent is to ensure that a “level playing field” is maintained, independent of the manufacturer, health care professional, or government agency, in data presentation to the subcommittee and in subcommittee determinations based on those data.

I would like to express my thanks to all members of and advisors to the working group that developed this document. In addition, I would like to thank Steve Brown, Janet Hindler, William Brasso, and Linda Miller for their helpful suggestions.

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Key Words and Phrases

Antimicrobial agents, standard dilution methods for bacteria that grow aerobically, standard disk diffusion test, standard reference method for anaerobes, susceptibility testing
Subcommittee on Antimicrobial Susceptibility Testing Mission Statement

The Subcommittee on Antimicrobial Susceptibility Testing is composed of representatives from the professions, government, and industry. Included among these are microbiology laboratory professionals, pharmacologists, health care providers and educators, representatives of government agencies, and experts from pharmaceutical and diagnostic microbiology industries. Using the CLSI voluntary consensus process, the subcommittee develops standards that promote accurate antimicrobial susceptibility testing and appropriate reporting.

The subcommittee’s ultimate mission is to provide useful information to enable laboratories to assist the clinician in the selection of appropriate antimicrobial therapy for patient care.

To accomplish this mission, the goals of the Subcommittee on Antimicrobial Susceptibility Testing are to:

• develop standard reference methods for antimicrobial susceptibility tests;
• provide quality control parameters for standard test methods;
• establish interpretive criteria for the results of standard antimicrobial susceptibility tests;
• provide suggestions for testing and reporting strategies that are clinically relevant and cost-effective;
• continually refine standards and optimize the detection of emerging resistance mechanisms through the development of new or revised methods, interpretive criteria, and quality control parameters;
• educate users through multimedia communication of standards and guidelines; and
• foster a dialogue with laboratories that use these methods and apply the interpretive criteria, as well as with clinicians who use the results of these tests as an integral part of patient management.

These guidelines are meant to be comprehensive and to include all antibacterial and antifungal agents for which the data meet established CLSI standards. The values that guide this mission are quality, accuracy, fairness, timeliness, teamwork, consensus, and trust.
Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters; Approved Guideline—Third Edition

1 Scope

Guidelines for interpretive criteria and quality control (QC) ranges are established by the Subcommittee on Antimicrobial Susceptibility Testing after review of extensive data. This guideline describes the data needed for such determinations. The document is intended for use by the subcommittee to ensure completeness of the data on which decisions are based, and to provide guidance to sponsors of antimicrobial agents preparing presentations requesting CLSI interpretive criteria and QC ranges for newly introduced agents, or to revise these for previously reviewed agents.

Guidelines presented in this document apply only to CLSI procedures and documents. The guidelines do not apply to antimicrobial agents that are used topically or for purposes other than inhibiting the growth of or killing microorganisms.

1.1 Guidelines for Antifungal Agents

This document was originally developed as guidance for determination of interpretive breakpoints for bacteria. Subsequently, the Subcommittee on Antifungal Susceptibility Testing has developed standardized methods that make it possible for laboratories to perform reliable and meaningful broth dilution and agar diffusion susceptibility testing of fungi (see CLSI documents M27, M38, and M44; and Pfaller et al10). Although differences may arise because of fungus-related limitations (eg, clinical data may be more limited than for bacteria, numbers of isolates available for testing may be limited for some relevant genera or species), the process of determination of interpretive breakpoints and QC for fungi is broadly the same as for the bacteria. Unless otherwise specifically noted herein, and making due allowance for our still evolving understanding of relevant differences for fungi, it may thus be assumed that the principles described in this document apply equally to antifungal agents.

As specific examples of this application, the Subcommittee on Antifungal Susceptibility Testing has described the derivation of breakpoints for voriconazole, fluconazole, and echinocandins by use of principles matching those of M23.10-13

2 Introduction

“The problem of extrapolating laboratory results to the clinical situation presents such a minefield of difficulties that microbiologists usually prefer to concentrate on obtaining reproducible estimates of antimicrobial susceptibility in the laboratory, using standardized methods, and to leave the problem of clinical relevance to the prescribing physician.”14 The preceding statement emphasizes that although the ideal goal of antimicrobial susceptibility testing (AST) is to predict the therapeutic efficacy of antimicrobial agents for infected patients, these in vitro tests do not always attain this goal. In vitro susceptibility tests are imperfect predictors of patient outcome for reasons both technical and clinical. Technical factors that affect susceptibility test results include but are not limited to the type of test method used, the inoculum size of the microorganism, the type of broth or agar medium used, the pH of the medium, the concentration of divalent cations, the incubation time and temperature, the growth phase of the microorganism, and the growth characteristics of the microorganism. CLSI addresses these factors through the CLSI consensus process and guidelines, but technical limitations remain. Clinical factors that affect the predictive value of antimicrobial susceptibility tests include the virulence of the infecting microorganism, whether the infection is localized or disseminated, whether the type of antimicrobial activity is inhibitory or microbicidal, the pharmacokinetic (PK) properties of the drug (achievable blood