CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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M23

Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters

This guideline discusses the necessary and recommended data for selecting appropriate breakpoints and quality control ranges for antimicrobial agents.

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

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Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters

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Abstract

Clinical and Laboratory Standards Institute guideline M23—*Development of* In Vitro *Susceptibility Testing Criteria and Quality Control Parameters* offers guidance for developing breakpoints and QC ranges for antimicrobial susceptibility tests against aerobic and anaerobic bacteria, as well as selected fungi, according to CLSI antimicrobial susceptibility testing standards. It describes the data used by the Subcommittees on Antimicrobial Susceptibility Testing and Antifungal Susceptibility Tests to establish these breakpoints and QC ranges for antimicrobial agents, including microbiological data, pharmacokinetic and pharmacodynamic characteristics, and clinical data. As antimicrobial agents are used in practice, additional experience accrued may be used to reassess breakpoints or QC ranges. Users of these guidelines should understand that susceptibility test results cannot predict clinical outcomes with absolute certainty. They should be used along with best clinical judgment and laboratory support to most effectively serve the patient.

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Foreword

CLSI develops standardized reference methods that measure the susceptibility of bacteria and fungi to antimicrobial agents *in vitro.* In this regard, the CLSI Subcommittee on Antimicrobial Susceptibility Testing (AST) is responsible for developing and updating the following CLSI susceptibility testing documents:

- M02—*Performance Standards for Antimicrobial Disk Susceptibility Tests*[1]
- M07—*Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*[2]
- M45—*Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria*[3]
- M11—*Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria*[4]
- M100—*Performance Standards for Antimicrobial Susceptibility Testing*[5] (supplement for M02,[1] M07,[2] and M11[4])

The CLSI Subcommittee on Antifungal Susceptibility Tests is responsible for developing and updating the following CLSI susceptibility testing documents:

- M27—*Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts*[6]
- M44—*Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts*[7]
- M60—*Performance Standards for Antifungal Susceptibility Testing of Yeasts*[8] (supplement for M27[6] and M44[7])
- M38—*Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi*[9]
- M51—*Method for Antifungal Disk Diffusion Susceptibility Testing of Nondermatophyte Filamentous Fungi*[10]
- M61—*Performance Standards for Antifungal Susceptibility Testing of Filamentous Fungi*[11] (supplement for M38[9] and M51[10])

M23 is an important foundation guideline that supports these susceptibility testing documents. M23's purpose is to provide guidance on the data submitted by sponsors and the procedures followed by the CLSI Subcommittee on AST to establish or revise QC ranges and susceptibility testing breakpoints for inclusion in CLSI documents. The process for determining breakpoints and QC ranges for antifungal agents is broadly the same as for the antibacterial agents, and the principles described in M23 also apply to antifungal agents.

This guideline recognizes that submissions may be made by a wide variety of organizations or individuals and that it is important to ensure the same processes are followed regardless of the data source. Nevertheless, it also recognizes that the extent of the data that can be provided to support new or revised breakpoints may vary significantly due to factors that include, but are not limited to, the age of the antimicrobial agent and whether the sponsor has access to raw data or only published data.

Essential Information

Content in this guideline marked with an asterisk (*) describes essential information required for review by the CLSI Subcommittee on AST. All chapters and subchapters without an asterisk describe additional information that may be supplied if available and that may be useful in supporting the selection of QC ranges and susceptibility testing breakpoints.

Overview of Changes

This guideline replaces the previous edition of the approved guideline, M23, 4th ed., published in 2016. Several changes were made in this edition, including:

- Deleted Subchapter 4.1.3 on publication of breakpoints that are different from those approved by the US Food and Drug Administration

- Added a new subchapter (Subchapter 4.4) that describes a new process for periodically reviewing established breakpoints

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

Key Words

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, including microbiology laboratories, government agencies, health care providers and educators, and 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 mission of the Subcommittee on Antimicrobial Susceptibility Testing is to:

- Develop standard reference methods for antimicrobial susceptibility tests.
- Provide quality control parameters for standard test methods.
- Establish breakpoints for the results of standard antimicrobial susceptibility tests and provide epidemiological cutoff values when breakpoints are not available.
- Provide suggestions for testing and reporting strategies that are clinically relevant and cost-effective.
- Continually refine standards and optimize detection of emerging resistance mechanisms through development of new or revised methods, breakpoints, and quality control parameters.
- Educate users through multimedia communication of standards and guidelines.
- Foster a dialogue with users of these methods and those who apply them.

The ultimate purpose of the subcommittee's mission is to provide useful information to enable laboratories to assist the clinician in the selection of appropriate antimicrobial therapy for patient care. The standards and guidelines are meant to be comprehensive and to include all antimicrobial agents for which the data meet established CLSI guidelines. 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

Chapter 1: Introduction

This chapter includes:

- Guideline's scope and applicable exclusions
- Background information pertinent to the guideline's content
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions
- Terms and definitions used in the guideline
- Abbreviations and acronyms used in the guideline

1.1 Scope

This guideline provides direction for determining breakpoints and QC parameters for antimicrobial agents that have a direct action on microorganisms. The intended audience includes sponsors (eg, antimicrobial agent manufacturers) planning to submit data to establish or revise QC ranges and susceptibility testing breakpoints and interpretive categories for inclusion in CLSI susceptibility testing documents. The methods described do not apply to:

- Slow-growing mycobacteria, for which specific guidance is available (see CLSI document M24[12])
- Antimicrobial agents formulated for direct administration to skin or mucous membranes or for inhalation
- Antimicrobial agents that are intended to exert activity within the gut lumen

Guidance presented in M23 applies only to CLSI procedures and documents.

1.2 Background

Susceptibility testing breakpoints, interpretive categories, and QC parameters are established by the CLSI Subcommittee on Antimicrobial Susceptibility Testing (AST) after comprehensive review of all available relevant data. This guideline describes the procedures to be followed by the CLSI Subcommittee on AST and by sponsors intending to submit data to facilitate timely review and decision-making processes. Data requirements to support setting new breakpoints and QC parameters and amendments to existing breakpoints are described.

The CLSI Subcommittee on AST has developed standardized methods that make it possible for laboratories to perform reliable and meaningful broth dilution and disk diffusion susceptibility testing of fungi (see CLSI documents M27,[6] M38,[9] M44,[7] and M51[10]). The process for determining breakpoints, interpretive categories, and QC ranges for antifungal agents is broadly the same as for the antibacterial agents. Thus, it may be assumed that the principles described in this guideline apply equally to antifungal agents. For this reason, the guideline refers to antimicrobial agents throughout. Where reference is made to the CLSI Subcommittee on AST, in most instances the same applies to the CLSI Subcommittee on Antifungal