This guideline discusses the necessary and recommended data 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.
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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 document M23—Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters offers guidance for developing interpretive criteria and QC ranges for antimicrobial susceptibility tests against aerobic and anaerobic bacteria, and selected fungi performed by CLSI antimicrobial susceptibility testing standards. It describes the data used by the Subcommittees on Antimicrobial Susceptibility Testing and Antifungal Susceptibility Tests to establish these interpretive criteria 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 interpretive criteria 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 the best clinical judgment and laboratory support to draw the best conclusions to 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 susceptibility testing documents:

M02—Performance Standards for Antimicrobial Disk Susceptibility Tests
M07—Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically
M45—Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria
M11—Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria
M100S—Performance Standards for Antimicrobial Susceptibility Testing

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

M27—Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts and corresponding supplement M27-S4
M38—Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi
M44—Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts and corresponding supplement M44-S3
M51—Method for Antifungal Disk Diffusion Susceptibility Testing of Nondermatophyte Filamentous Fungi and corresponding supplement M51-S1

M23 is an important foundation document that supports these susceptibility testing standards. The purpose of M23 is to provide guidance on the data submitted by sponsors and the procedures followed by the Subcommittee on AST to establish or revise QC ranges and susceptibility testing interpretive criteria for inclusion in CLSI documents. The process of determination of interpretive criteria 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.

The document recognizes that submissions may be made by a wide variety of organizations or individuals, and it is important to ensure that the same processes are followed regardless of the data source. Nevertheless, it recognizes that the extent of the data that can be provided to support new or revised interpretive criteria may be very variable 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.

Since the previous edition of this document, several changes have been made to the working practices of the CLSI Subcommittee on AST with the intent to streamline procedures for handling submissions. These changes include:

- A new structure of standing working groups
- Formation of ad hoc working groups convened by the Chairholder of the CLSI Subcommittee on AST and by working group chairholders as necessary to facilitate the review of individual submissions

M23 has been revised to reflect these important revisions to working practices.

In particular, Chapter 4 provides a full description of the procedures that have been implemented in recent years for the handling of requests to determine new or to revise existing interpretive criteria.

The processes to be followed have been established since the previous edition of this document. These processes have facilitated close cooperation between the CLSI Subcommittee on AST and the US Food and
Drug Administration based on a clear understanding of procedures that the CLSI Subcommittee on AST will follow in the various scenarios that may occur.

In recent years, the relative importance of analyses of pharmacokinetic-pharmacodynamic (PK-PD) relationships for identifying clinically relevant interpretive criteria has continued to increase. Reflecting the advances that have been made in the field of pharmacometrics since the previous edition of this document, this edition contains a completely revised chapter (Chapter 5) on minimal inhibitory concentration (MIC) interpretive criteria. This chapter contains:

- Information regarding the identification of nonclinical PK-PD cutoffs and clinical exposure-response cutoffs
- Epidemiological cutoff values and clinical cutoffs
- Approaches to selecting MIC interpretive criteria when various combinations of these cutoffs are available for review

Finally, I would like to express my thanks to the members of the Working Group on AST Criteria and QC Parameters who participated in drafting this document, in particular the Vice-Chairholder, Kerry Snow; to the Working Group on PK-PD for drafting much of Chapter 5, in particular the Chairholder, Linda Miller; and to the Working Group on Quality Control for revising Chapter 3, in particular the Co-Chairholder, Sharon Cullen.

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**Essential Information**

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

**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, healthcare 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 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 detection of emerging resistance mechanisms through development of new or revised methods, interpretive criteria, 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 \textit{In Vitro} Susceptibility Testing Criteria and Quality Control Parameters

Chapter 1: Introduction

This chapter includes:

- Document scope and applicable exclusions
- Background information pertinent to the document content
- “Note on Terminology” that highlights particular use and/or variation in use of terms and/or definitions
- Terms and definitions used in the document
- Abbreviations and acronyms used in the document

1.1 Scope

This document provides guidance for determination of interpretive criteria and QC parameters for antimicrobial agents that have a direct action on microorganisms. The methods described do not apply to:

- Slow-growing mycobacteria, for which specific guidance is available (see CLSI document M24\textsuperscript{13})
- 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 this document applies only to CLSI procedures and documents.

1.2 Background

Susceptibility testing interpretive criteria and QC parameters are established by the 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 are described to support setting new interpretive criteria and QC parameters and amendments to existing criteria.

The Subcommittee on AST 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\textsuperscript{,6} M38\textsuperscript{,8} M44\textsuperscript{,9} and M51\textsuperscript{11}). The process of determination of interpretive criteria 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 document apply equally to antifungal agents. For this reason, the document refers to antimicrobial agents throughout. Where reference is made to the CLSI Subcommittee on AST, in most instances the same applies to the Subcommittee on Antifungal Susceptibility Tests. At the time of M23’s publication, a CLSI document on the criteria for development and use of epidemiological