
Systemic Antibacterial and Antifungal Drugs: Susceptibility Test Interpretive Criteria Labeling for NDAs and ANDAs Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**December 2017
Labeling**

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Systemic Antibacterial and Antifungal Drugs: Susceptibility Test Interpretive Criteria Labeling for NDAs and ANDAs Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

- This guidance provides recommendations on fulfilling the new labeling requirements for susceptibility test interpretive criteria for prescription systemic antibacterial and antifungal drugs as established by section 3044 of the 21st Century Cures Act (Cures Act) (Public Law 114-255).²
- This guidance describes FDA's recommendations on (1) how to make these labeling changes for antimicrobial drugs with approved new drug applications (NDAs) or abbreviated new drug applications (ANDAs), (2) language to remove from the labeling of such drugs, and (3) labeling language to use for all antimicrobial drugs to reference the FDA's Susceptibility Test Interpretive Criteria web page.³
- This guidance supersedes sections I, II(B), III, and IV of the guidance for industry *Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices*.⁴

¹ This guidance has been prepared by the Office of Antimicrobial Products in the Center for Drug Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2017-D-6821 (available at <https://www.regulations.gov/docket?D=FDA-2017-D-6821>) (see the instructions for submitting comments in the docket).

² Consistent with the Cures Act, for the purposes of this guidance, all references to *antimicrobial drugs* refers to systemic antibacterial and antifungal drugs. See section 511A(f)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Currently, biological products, as defined in section 351 of the Public Health Service Act, are not included in the definition of antimicrobial drug for purposes of section 511A of the FD&C Act. Under section 511A(f)(4)(B), FDA may, by regulation, add certain biological products to the definition of antimicrobial drug.

³ See the FDA Susceptibility Test Interpretive Criteria (Interpretive Criteria) web page at <https://www.fda.gov/STIC>.

⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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- In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

- Antimicrobial susceptibility testing is used to determine if certain microorganisms isolated from a patient with an infection are likely to be killed or inhibited by a particular antimicrobial drug. Historically, susceptibility test interpretive criteria have been contained in the *Microbiology* subsection of antimicrobial drug labeling. There have been significant challenges associated with ensuring that this information is up to date in antimicrobial drug labeling.
- Section 3044 of the Cures Act added section 511A to the Federal Food, Drug and Cosmetic Act (FD&C Act). Section 511A clarifies FDA's authority to identify and efficiently update susceptibility test interpretive criteria for antimicrobial drugs. This authority includes FDA's recognition of standards established by standards development organizations. Section 511A(b) states that FDA retains full authority to accept a standard in whole or in part or to establish alternative susceptibility test interpretive criteria. Section 511A also clarifies that sponsors of antimicrobial susceptibility test devices may rely upon these FDA-recognized or listed susceptibility interpretive criteria to support premarket authorization of their devices so long as certain conditions are met. This provides for a more streamlined process for incorporating up-to-date information about antimicrobial susceptibility into the labeling for such devices.
- Section 511A(b) of the FD&C Act required FDA to establish a Susceptibility Test Interpretive Criteria (Interpretive Criteria) web page within one year of enactment of the Cures Act. This web page contains a list of FDA-recognized susceptibility test interpretive criteria standards, as well as other susceptibility test interpretive criteria identified by FDA. See the FDA Susceptibility Test Interpretive Criteria web page at <https://www.fda.gov/STIC>.
- At least every six months, FDA will publish on the Interpretive Criteria web page a notice that does the following:
 - Recognizes new or updated susceptibility test interpretive criteria standards or parts of standards
 - Withdraws recognition of susceptibility test interpretive criteria standards or parts of standards

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- Makes any other necessary updates to the lists published on the Interpretive Criteria web page
- In addition, FDA will update the Interpretive Criteria web page with susceptibility test interpretive criteria upon approval of an NDA for an antimicrobial drug, as appropriate.
- Section 511A(d)(1) of the FD&C Act requires that, within one year of establishment of the Interpretive Criteria web page, all application holders of antimicrobial drugs legally marketed before the establishment of the Interpretive Criteria web page⁵ remove the susceptibility test interpretive criteria information, if any, and related information from approved labeling and replace the criteria with a reference to the Interpretive Criteria web page.⁶
- Section 511A(d)(2) of the FD&C Act requires all antimicrobial drugs approved on or after the date of establishment of the Interpretive Criteria web page to include in labeling a reference to the Interpretive Criteria web page in lieu of susceptibility test interpretive criteria and related information. See section III.B., Information to Be Added to Antimicrobial Drug Labeling.⁷

III. LABELING RECOMMENDATIONS

A. Information to Be Removed from Antimicrobial Drug Labeling

- Holders of approved applications should remove the following information from the labeling of approved antimicrobial drugs within one year of the date of the establishment of the Interpretive Criteria web page, December 13, 2017:

⁵ The requirements under section 511A(d)(1) apply to **all** antimicrobial drugs approved before the establishment of the Interpretive Criteria web page, which includes antimicrobial drug products that are approved under both NDAs and ANDAs.

⁶ Under section 502(dd) of the FD&C Act, as added by Section 3044(b)(2) of the Cures Act, an antimicrobial drug is misbranded if its labeling fails to conform to the labeling requirements under section 511A(d) of the FD&C Act.

⁷ In general, FDA requires that ANDAs include information to show that the labeling proposed for the generic drug is the same as the labeling approved for the reference listed drug (RLD) except for changes required because of differences approved under a suitability petition (see section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93) or because the generic drug and the RLD are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the FD&C Act). FDA implementing regulations include examples of permissible labeling differences that may result because the generic drug and RLD are produced or distributed by different manufacturers (21 CFR 314.94(a)(8)(iv)). One such permissible difference is labeling revisions made to comply with current FDA labeling guidelines or other guidance (21 CFR 314.94(a)(8)(iv)). For ANDAs approved after the implementation of the Interpretive Criteria web page, if the ANDA holder submits proposed labeling changes to comply with the requirements of section 511A of the FD&C Act and the current RLD labeling does not include these labeling changes, FDA may consider such differences in labeling between the generic drug and RLD to be permissible differences in labeling under FDA's authorities. See generally, sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94.

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- Information on susceptibility test interpretive criteria and associated test methods and quality control standards in the *Microbiology* subsection of the CLINICAL PHARMACOLOGY section, generally under the headings Susceptibility Test Methods and Quality Control.
- Related citations included in the REFERENCES section.
- For antimicrobial drugs approved following the establishment of the Interpretive Criteria web page, susceptibility test interpretive criteria and related information should not be included in the *Microbiology* subsection of the CLINICAL PHARMACOLOGY section of labeling, except as described in Section III.B., Information to Be Added to Antimicrobial Drug Labeling.⁸

B. Information to Be Added to Antimicrobial Drug Labeling

- FDA recommends that antimicrobial drugs, including those approved following the establishment of the Interpretive Criteria web page, contain the following statement in the *Microbiology* subsection of the CLINICAL PHARMACOLOGY section of labeling, in lieu of the previously listed susceptibility test interpretive criteria and related information:

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

C. Information to Be Retained in Antimicrobial Drug Labeling

- Section 511A of the FD&C Act only applies to the information in labeling describing susceptibility test interpretive criteria and associated test methods and quality control standards with associated references for antimicrobial drugs. All other guidance, regulations, and statutory requirements remain applicable.
- Section 511A of the FD&C Act does not affect the antimicrobial drug labeling information within the *Microbiology* subsection of the CLINICAL PHARMACOLOGY section on Mechanism of Action, Resistance, Interactions With Other Antimicrobials, and Antimicrobial Activity, which includes the first and second lists of target bacteria, or other information in antimicrobial drug labeling other than the susceptibility test interpretive criteria, associated test methods, and quality control standards, with associated references.⁹

⁸ Section 511A(d) of the FD&C Act.

⁹ For more information about labeling antimicrobial drugs, see the guidance for industry *Microbiology Data for Systemic Antibacterial Drugs — Development, Analysis, and Presentation*.

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IV. REPORTING LABELING CHANGES

- As mentioned above, **all** holders of approved antimicrobial drug applications under section 505 of the FD&C Act (i.e., both NDAs and ANDAs), as applicable, are required to submit updated labeling consistent with section III., Labeling Recommendations, within one year of the establishment of the Interpretive Criteria web page.¹⁰
- As described in section 511A(d)(1)(B) of the FD&C Act, such labeling changes are considered to be minor changes under 21 CFR 314.70 that can be reported in the application holder's next annual report.¹¹ Although not required, an application holder can report the labeling changes in a supplement to an approved application.
- FDA strongly encourages an application holder to identify in the cover letter of the annual report, or in the supplement containing the changes, that the enclosed submission fulfills the requirements of section 511A(d)(1) of the FD&C Act.¹²

V. PAPERWORK REDUCTION ACT OF 1995

This guidance refers to previously approved collections of information found in FDA regulations. The collections of information are subject to review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR 201.56(a)(2) have been approved under OMB Control No. 0910-0572; the collections of information in 21 CFR 314.70(b)(2)(v) and 314.81(b)(2)(i) have been approved under OMB Control No. 0910-0001.

¹⁰ See section 511A(d)(1) of the FD&C Act.

¹¹ Application holders for drug products approved under section 505(j) of the FD&C Act may submit labeling changes to comply with the requirements under section 511A(d)(1) as part of the next annual report even if such changes are not reflected in the last approved labeling for the respective RLD.

¹² If the application holder submits the labeling changes to comply with the requirements of section 511A of the FD&C Act as part of a labeling supplement to an already approved ANDA and the labeling changes are not reflected in the last approved labeling for the respective RLD, FDA may consider the labeling changes proposed by the ANDA holder to be permissible differences in labeling under FDA's authorities. See generally, sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94 and 21 CFR 314.127.

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**APPENDIX:
EXAMPLE FORMAT FOR SUSCEPTIBILITY TEST
INTERPRETIVE CRITERIA LABELING**

Per changes to labeling requirements for antimicrobial drugs under section 511A of the Federal Food, Drug, and Cosmetic Act, the following is an example of recommended language to be removed in drug labeling and sample replacement text with additional FDA recommendations in italics. For more information concerning this section of labeling, see the guidance for industry *Microbiology Data for Systemic Antibacterial Drugs — Development, Analysis, and Presentation*.¹

12 CLINICAL PHARMACOLOGY

12.4 Microbiology

Mechanism of Action

Resistance

Interaction With Other Antimicrobials

Antimicrobial Activity

Susceptibility Testing

Remove information on susceptibility test interpretive criteria and associated test methods and quality control standards found generally under the headings Susceptibility Test Methods and Quality Control, and add the following statement:

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

The following is sample text that would be removed from existing approved labeling of an antimicrobial drug:

~~When available, the clinical microbiology laboratory should provide cumulative reports of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas as periodic reports that describe the susceptibility profile of nosocomial and community acquired pathogens. These reports should aid in the selection of an appropriate antibacterial drug for treatment.~~

¹ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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Dilution Techniques

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method^{1,2} (broth and/or agar). The MIC values should be interpreted according to criteria provided in Table [insert table number].

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.^{2,3} This procedure uses paper disks impregnated with [x] mcg [name of drug] to test the susceptibility of bacteria to [name of drug]. The disc diffusion breakpoints are provided in Table [insert table number].

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to [name of drug] can be determined by a standardized test method.⁴ The MIC values obtained should be interpreted according to the criteria provided in Table [insert table number].

Table [insert table number]. Susceptibility Test Interpretive Criteria for [name of drug]

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)				Disk Diffusion (zone diameters in mm)		
	S	I	R		S	I	R
Pathogen #1	<#	#—#	≥#		≥#	#—#	<#
Pathogen #2	<#	#—#	≥#		≥#	#—#	<#
etc.	etc.				etc.		

A report of *Susceptible (S)* indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *Intermediate (I)* indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of the drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant (R)* indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the infection site; other therapy should be selected.

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Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.^{1,2,3,4} Standard [name of drug] powder should provide the following range of MIC values noted in Table [insert table number]. For the diffusion technique using the [disk content of antimicrobial] mcg disk, the criteria in Table [insert table number] should be achieved.

Table [insert table number]. Acceptable Quality Control Ranges for [name of drug]

	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
QC strain #1	#–#	#–#
QC strain #2	#–#	#–#
etc.	etc.	etc.

15 REFERENCES

Retain and renumber any references not related to susceptibility testing.

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—[Edition]. CLSI document M07 [Edition number]. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087, USA, [Year].
2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; [Supplement Edition]. CLSI document M100 [Supplement Edition number]. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087, USA, [Year].
3. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests: Approved Standard—[Edition]. CLSI document M02—[Edition number]. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087, USA, [Year].
4. Clinical and Laboratory Standards Institute (CLSI). Methods for Antimicrobial Testing of Anaerobic Bacteria; [Edition]. CLSI document M11 [Edition number]. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087, USA, [Year].