Guidance for Industry

Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices

DRAFT GUIDANCE

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

June 2008
Labeling

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TABLE OF CONTENTS

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to inform industry of how the FDA intends to comply with section 1111 of the Food and Drug Administration Amendments Act (FDAAA), which requires FDA to identify and periodically update susceptibility test interpretive criteria[2] for antibacterial drug products and to make those findings publicly available. Because susceptibility test interpretive criteria, susceptibility test methods, and quality control parameters are interrelated, this guidance addresses procedures for updating all three of these elements of labeling of antibacterial drug products for human use. The guidance is also intended to remind drug application holders of their responsibility to update this information in the labeling of their antibacterial drug products (see 21 CFR 201.56(a)(2)). In addition, this guidance provides directions to manufacturers of antimicrobial susceptibility testing (AST) devices for updating labeling regarding susceptibility testing information.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should

[1] This guidance has been prepared by the Office of Antimicrobial Products in the Center for Drug Evaluation and Research (CDER) and the Office of In Vitro Diagnostic Device Evaluation and Safety in the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

[2] Section 1111 of FDAAA uses the term *clinically susceptible concentrations* and defines that term as "specific values which characterize bacteria as clinically susceptible, intermediate, or resistant to the drug (or drugs) tested" (Public Law 110-85). Because the term is more commonly used in clinical microbiology laboratories, FDA uses the term *susceptibility test interpretive criteria* to describe the drug concentrations where a type of bacteria is categorized as susceptible, intermediate, or resistant. Therefore, throughout this guidance, we use the term *susceptibility test interpretive criteria* rather than the statutory term *clinically susceptible concentrations*, but we intend for these two terms to have the same meaning.

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

On September 27, 2007, the President signed FDAAA into law. Section 1111 of FDAAA requires FDA to identify and periodically update susceptibility test interpretive criteria for antibacterial drug products and to make those findings publicly available.[3] By enacting section 1111 of FDAAA, Congress recognized the importance of maintaining updated susceptibility test interpretive criteria.[4]

A. The Importance of Susceptibility Test Interpretive Criteria

Antibacterial susceptibility testing is used to determine if bacteria that are isolated from a patient with an infection are likely to be killed or inhibited by a particular antibacterial drug product at the concentrations of the drug that are attainable at the site of infection using the dosing regimen(s) indicated in the drug product's labeling. The results from antibacterial susceptibility testing generally categorize bacteria as "susceptible," "intermediate," or "resistant" to each of the antibacterial drugs that are tested.[5] When available, culture and susceptibility testing results are one of the factors that physicians consider when selecting an antimicrobial drug product for treating a patient.

The numerical values generated by susceptibility testing to determine whether a particular microorganism is susceptible to a particular antimicrobial drug — the antimicrobial susceptibility test interpretive criteria — are commonly referred to as *breakpoints*. These *breakpoints* are specified in the antimicrobial drug product's label. The antimicrobial susceptibility test interpretive criteria can be used to interpret results from either manual or automated AST devices.

For labeling AST devices, CDRH, the component of FDA that regulates AST devices, recognizes the importance of having antimicrobial susceptibility test interpretive criteria that are consistent with antimicrobial drug product labeling.[6] However, in cases where antibacterial drug product labels are out-of-date, AST devices sometimes have inconsistent labeling.

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[3] This guidance applies to systemic antibacterial drug products for human use. We note that susceptibility test interpretive criteria have not been developed for nonsystemic antibacterial drug products because the dosing is less precise and typically involves local exposure of the infected area to high concentrations of the antibacterial agents.

[4] FDA notes that the accuracy of susceptibility test interpretive criteria is dependent on the application of appropriate test methods and associated quality control parameters.

[5] We also note that in circumstances where criteria for intermediate and/or resistant bacteria have not been established, bacteria categorized as other than "susceptible" are referred to as "nonsusceptible."

[6] See March 5, 2007, response to the June 21, 2006, citizen petition from the Clinical Laboratory Standards Institute, Docket No. 2006P-0271 available at http://www.fda.gov/ohrms/dockets/dockets/06p0271/06p0271.htm.

Inconsistencies between antibacterial drug product labels and AST device labels are not desirable. Having up-to-date labeling for antibacterial drug products will better ensure the consistency of antibacterial drug and AST device labels.

B. Antibacterial Drug Product Labeling

FDA regulations require that information on susceptibility testing be included in the labeling for antibacterial drug products (see 21 CFR 201.57(c)(2)(i)(C)). The INDICATIONS AND USAGE section of labeling for antibacterial drugs includes the condition(s) for which the product has been found to be safe and effective if used as described in the product labeling. The INDICATIONS AND USAGE section also includes a list of specific microbial organisms for the particular indicated condition(s). The results from culture and susceptibility testing can be used to guide appropriate selection of an antibacterial drug product.

In general, FDA currently establishes susceptibility test interpretive criteria in the context of an individual new drug application (NDA), and corresponding information is included in the approved labeling for the drug product, based on in vivo and in vitro information provided by the applicant. Specific information on susceptibility test interpretive criteria, and associated test methods and quality control standards, is generally included in the *Microbiology* subsection of the CLINICAL PHARMACOLOGY section of labeling. The labeling informs health care providers on appropriate use of the antibacterial drug product when culture and susceptibility test results are available. Generally, drug product labeling is publicly available at the DailyMed Web site or at the Drugs@FDA Web site.[7]

Over time, additional information may become available and/or changes may occur regarding the susceptibility of certain bacteria to antibacterial drugs. For example:

- Additional data on susceptibility of bacteria and response to therapy may show decreased susceptibility of bacteria to a particular antibacterial drug. Furthermore, the development of new mechanisms of resistance in bacteria may result in decreased susceptibility to a particular antibacterial agent. Changes in susceptibility may raise efficacy or safety concerns when out-of-date susceptibility test information is used in guiding treatment of patients with the indicated infection(s).

- Microbiological methods and quality control standards may be refined to improve performance or better assess the quality control of susceptibility testing.

Consequently, it is important that the in vitro susceptibility test methods, the susceptibility test interpretive criteria, and the quality control parameters listed in the labeling for a product be reviewed on a regular basis and updated to reflect the most current information.

Although sponsors are required to update susceptibility test interpretive criteria when appropriate, FDA has found it difficult to ensure that the labeling of a number of antibacterial

[7] DailyMed can be accessed at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Product labeling is also available on the Drugs@FDA Web site at http://www.accessdata.fda.gov/scripts/cder/drugsatfda.

drugs and the associated AST devices is current. Before the information in the *Microbiology* subsection in the drug labeling can be changed, the application holder, in general, has to submit an appropriate labeling supplement to the Agency for review and approval. An internal review of the *Microbiology* subsection of labeling for a large number of antibacterial drug products confirmed that the product labeling often contains susceptibility test methods, antimicrobial susceptibility test interpretive criteria, and/or quality control parameters that have not been updated in many years. Also, FDA has received citizen petitions requesting that the susceptibility test interpretive criteria for specific drug products be updated. FDA is also aware that information in the *Microbiology* subsection of product labeling is sometimes inconsistent with the standards relied on by many microbiology laboratories. This guidance document addresses concerns about these inconsistencies.

III. SECTION 1111 OF FDAAA AND HOW FDA INTENDS TO COMPLY

Section 1111 took effect immediately when FDAAA was signed into law by the President (September 27, 2007). The specific language of section 1111(b) requires FDA to "identify (where such information is reasonably available) and periodically update" susceptibility test interpretive criteria. Section 1111(c) requires FDA to make susceptibility test interpretive criteria publicly available "not later than 30 days after the date of identification and any update under . . . section [1111]."

FDA's approach for updating susceptibility test interpretive criteria in the manner described in this guidance will comply with Section 1111. FDA is using other sources, in addition to applicant-initiated drug product labeling, to identify and update susceptibility test interpretive criteria, and associated test methods and quality control parameters, particularly if the antibacterial drug product labeling is out of date. Potentially useful sources for this information are existing standards established by nationally or internationally recognized standard development organizations.

Where appropriate, FDA intends to recognize susceptibility test interpretive criteria, and associated test methods and quality control parameters, by publishing annually in a *Federal Register* notice certain standards developed by one or more nationally or internationally recognized standard development organizations.[8] This approach is consistent with FDA's current authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360d(c)) to recognize a standard for devices by issuing a *Federal Register* notice. FDA intends to combine our recognition of standards for use in both antibacterial drug product labeling and AST devices.[9] Under this approach, FDA retains the authority to accept or reject for recognition (based on our scientific judgment) of any susceptibility test interpretive criteria, or associated susceptibility test method or quality control parameters, developed by a standard development organization for a specific bacterium treated by a specific approved antibacterial drug product.

[8] The standards recognized by FDA will be available through a public source, such as the National Library of Medicine (Bethesda, MD).

[9] This guidance describes the procedures for FDA to recognize a standard for antibacterial drug product labeling and related AST devices. Under section 514(c) of the Act, FDA has authority to recognize a standard for use by device manufacturers for other purposes. The procedures for devices are described, in general, in a separate guidance from CDRH on *Recognition and Use of Consensus Standards* available at http://www.fda.gov/cdrh/guidance.html.

Applicants and manufacturers have the option to rely on the FDA recognized standards as one approach to updating their product labeling (see sections III.B and section IV). FDA's final decision regarding the appropriate susceptibility test information for a particular drug product will be publicly available in approved product labeling (see section III.F).

IV. UPDATING SUSCEPTIBILITY TEST INFORMATION IN ANTIBACTERIAL DRUG PRODUCT LABELING

A. Periodic Evaluation of Information in the *Microbiology* Subsection

Holders of new drug applications (NDAs) and those abbreviated new drug applications (ANDAs) that are designated as a reference listed drug (RLD), for systemic antibacterial drug products should review their product labeling at least annually to evaluate whether the *Microbiology* subsection is up to date. When FDA recognizes a standard that is different from the information in the *Microbiology* subsection of the labeling for the application holder's product, the differences should be specifically evaluated by the applicant (§ 201.56(a)(2)). Not later than 60 days after FDA publicly recognizes a standard that is relevant to the application holder's product, the application holder should submit updated labeling (see section III.B) or provide a written explanation why it believes the standard is not applicable to its antibacterial drug product (see section III.C).

B. Approaches to Updating the Labeling

This guidance describes two approaches for application holders to update labeling as follows:

- updating information in the *Microbiology* subsection of product labeling by submitting revised product labeling that is in conformance with a standard that has been recognized by the Agency

  or

- submitting data that support a change in the information in the *Microbiology* subsection of product labeling that differs from the Agency's recognized standard.

Either approach can be a suitable and sufficient route for application holders to provide information to FDA for review by the FDA to determine the appropriate updating of the *Microbiology* subsection in product labeling.

1. Updating Through Reliance on a Standard Recognized by the FDA

If the standards recognized in the *Federal Register* notice differ from the information in an applicant's current product labeling, the applicant can submit proposed labeling to the Agency that is in conformance with the FDA recognized standards. The applicant should submit a prior approval labeling supplement containing the appropriate changes not later than 60 days after the publication of the *Federal Register* notice.

The applicant should clearly state that the purpose of the labeling supplement is to change the *Microbiology* subsection of labeling in conformance with an FDA recognized standard and cite

the relevant *Federal Register* notice in which the standard is recognized. Labeling changes referencing an FDA recognized standard should not be combined with any other "Changes Being Effected (CBE)" or "Prior Approval" labeling revisions being submitted.

2. Updating Through Submission of Information that Supports Labeling Different from a Standard Recognized by FDA

Application holders who wish to update their product's labeling with susceptibility test information that differs from the standards that the FDA recognizes in the *Federal Register* should submit proposed labeling as a supplement to their application, not later than 60 days after the publication of the *Federal Register* notice. The applicant should submit a prior approval labeling supplement containing any proposed change to the *Microbiology* subsection, along with information that supports a change to the susceptibility test interpretive criteria and associated in vitro susceptibility test methods and/or quality control parameters.

The applicant should clearly state that the purpose of the labeling supplement is to change the *Microbiology* subsection based on the submitted information. This labeling supplement should not be combined with any other "Changes Being Effected (CBE)" or "Prior Approval" labeling revisions being submitted.

Even if FDA has not recognized a standard with different susceptibility test interpretive criteria and associated in vitro susceptibility test methods and/or quality control parameters for a specific drug, applicants can update their labeling by providing additional information to support the proposed change. Application holders should submit a prior approval labeling supplement whenever they have information that indicates the *Microbiology* subsection of their product labeling needs to be updated.

C. If the Applicant Believes No Change to the Labeling Is Needed

If the information in the applicant's product labeling differs from the standards recognized by the Agency and the applicant believes that changes to the labeling are not needed, the applicant should provide written justification to the FDA not later than 60 days after the publication of the *Federal Register* notice. For example, additional scientific information may justify not applying the recognized standard to an applicant's specific drug product. An applicant who believes a change in the product labeling is not needed should submit the justification as general correspondence to its application. The applicant should clearly state that the purpose of the correspondence is to provide a justification for not changing the *Microbiology* subsection of labeling in accordance with an FDA recognized standard.

D. Addressing the Status of the *Microbiology* Subsection in the Annual Report

Application holders should also include in their annual report an assessment of whether the information in the *Microbiology* subsection of their product labeling is current or changes are needed (21 CFR 314.81(b)(2)(i)).

E. The Labeling Submission

All supporting documents (including current package insert) for revision of the labeling should be included in the submission. Submit the revised content of labeling (21 CFR 314.50(1)(l)(i)) in structured product labeling (SPL) format.[10]

F. Public Availability of Updated *Microbiology* Subsection Labeling

Section 1111(c) requires FDA to make susceptibility test interpretive criteria publicly available not later than 30 days after the date of identification and any update. As described in section II.C of this guidance, FDA intends to issue annually a *Federal Register* notice recognizing appropriate susceptibility test interpretive criteria, quality control parameters, and methods developed by one or more nationally or internationally recognized standard development organizations. The *Federal Register* notice will provide references to the standards recognized by the Agency, but will not describe individual susceptibility test interpretive criteria for each approved drug product. The susceptibility test interpretive criteria will be available from the standard development organization(s).

Because drug application holders can choose different approaches for responding to the notice of FDA recognized standards, FDA will consider the key date under FDAAA for identification and update of susceptibility test interpretive criteria to be the date the Agency approves a labeling supplement for an antibacterial product. Approved updated product labeling for antibacterial drug products will be made publicly available at the Drugs@FDA Web site or at the DailyMed Web site.[11] Antibacterial drug labeling with updated information on susceptibility test interpretive criteria in the *Microbiology* subsection will be posted on one of these public Web sites within 30 days of an approval action for the application holder's labeling supplement that effects the change.

V. UPDATING SUSCEPTIBILITY TEST INFORMATION FOR IN VITRO DIAGNOSTIC AST DEVICES

As described above, FDA intends to recognize susceptibility test interpretive criteria (see section III of this draft guidance). Once FDA has recognized a standard, NDA holders should update their drug labeling and FDA will make the approved, updated drug labeling publicly available. If the susceptibility test interpretive criteria in the labeling for an AST device are inconsistent with the updated drug labeling, AST manufacturers should update their labeling to be consistent with this new, publicly available drug labeling. We recommend that AST manufacturers update their labeling at the first label reprinting after the updated drug labeling is made public.

While updating the susceptibility test interpretive criteria will significantly affect the safety and effectiveness of the AST device and, therefore, ordinarily would require submission of a

[10] See http://www.fda.gov/oc/datacouncil/spl.html.

[11] DailyMed can be accessed at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Product labeling is also available on the Drugs@FDA Web site at http://www.accessdata.fda.gov/scripts/cder/drugsatfda.

premarket notification (510(k)) prior to updating device labeling (21 CFR 807.81(a)(3)(i)), FDA intends to exercise enforcement discretion with regard to submission of a new 510(k) in certain circumstances. To determine whether a particular AST device is within the scope of FDA's intended exercise of enforcement discretion, manufacturers should perform a comparative study that demonstrates whether the updated susceptibility test interpretive criteria affect performance of the device. If the updated interpretive criteria do not affect device performance, as described in *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA* (the Class II special controls guidance),[12] and the only change to the AST labeling is updating susceptibility test interpretive criteria, then FDA intends to exercise enforcement discretion with regard to the 510(k) requirement and the manufacturer may change its AST labeling without submitting a 510(k). If the updated susceptibility test interpretive criteria change the device performance, and the manufacturer will update the interpretive criteria and change the device performance portion of the labeling, then the device manufacturer should submit a new 510(k) with the results of the comparative study. See the Class II special controls guidance referenced above for information on acceptable device performance. The comparative study should incorporate the following design elements:

- follow the design for the comparative study described in the Class II special controls guidance
- use a similar group of organisms as those groups that provided the original Essential Agreement or Category Agreement results
- include a representative number from all groups of organisms that might be affected by modifications to the device

Manufacturers can report the results using the table format examples provided in the Class II special controls guidance. Please contact the Division of Microbiology Devices, Office of In Vitro Diagnostic Device Evaluation and Safety, at CDRH for details on the extent of the data to be submitted.

[12] The *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry* is available at http://www.fda.gov/cdrh/oivd/guidance/631.pdf. FDA intends to update the Class II special controls guidance document to incorporate the information above.