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6 November 1998

Food and Drug Administration
Dockets Management Branch
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

Re: Docket Number 98N-0339

The following comments are provided by NCCLS as stakeholder input to FDA on the matters described below.

BACKGROUND ON NCCLS

NCCLS is an organization of health professional, government, and industry groups established in 1968 to develop a formal consensus process for standardization in the clinical laboratory. The Food and Drug Administration is a member organization. The program has expanded greatly in the past 30 years --- NCCLS's broad program aims to enhance the value of all medical testing through the development and dissemination of standards, guidelines, and best practices. NCCLS benefits the public and its professional, government, and industry constituencies by:

- providing professionals information to have the appropriate services performed correctly;
- supporting the efforts of responsible bodies to assure the quality of products and practices; and
- facilitating the development and availability of useful, accurate, medical services.

NCCLS's goal is to improve the quality of medical testing and healthcare services; its method is the consensus process. The NCCLS process is defined as a careful system of development, evaluation, and continued scrutiny at multiple levels to ensure the widest possible consensus. Checks and balances assure that dissenting opinions are given full consideration at all stages of the study, review, and voting periods required to achieve consensus and adopt a standard or guideline.

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In 1977, NCCLS was accredited by the American National Standards Institute (ANSI) as a voluntary consensus standards organization.

First designated in 1985, NCCLS was redesignated a World Health Organization Collaborating Center for Clinical Laboratory Standards in 1992 and again in 1997. NCCLS actively promotes global harmonization of standards through its own initiatives and through direct communication links and cooperative agreements with many standards-setting organizations around the world. NCCLS encourages use of its standards as resources in the development of international and regional standards. Since 1994, NCCLS has managed the International Organization for Standardization (ISO) Technical Committee on Clinical laboratory testing and in vitro diagnostic test systems (ISO/TC 212).

In just over 30 years, NCCLS has evolved into an organization of over 2,000 member organizations and over 2,000 volunteers who have produced hundreds of consensus standards.

CURRENT NCCLS EFFORTS TO SUPPORT FDA

NCCLS has been able to help FDA with one specific aspect of the FDA Modernization Act --- the recognition of voluntary consensus standards by the Center for Devices and Radiological Health.

Almost 50 NCCLS consensus documents, to date, have been recognized by FDA. A manufacturer's assertion of conformance to these standards would be sufficient for FDA to avoid expending resources to review the supporting data, thereby streamlining the review process.

Clearly this addresses directly the Agency's request for recommendations to meet its statutory obligations to achieve timely product reviews. NCCLS will continue to work with FDA's Center for Devices and Radiological Health to identify more and better consensus standards useful in reducing the amount of information manufacturers need to submit and FDA's staff needs to review.

NEW PROPOSAL FOR NCCLS WORK TO ASSIST FDA

As part of its efforts to implement the FDA Modernization Act, FDA has reached out to its stakeholders seeking input to a plan for complying with each of the Agency's obligations under the Federal Food, Drug, and Cosmetic Act. This plan is to include six objectives: maximize the availability of information about FDA's processes, ditto for information about new

products, meet inspection and postmarketing obligations, ensure access to needed scientific and technical expertise, meet review timeframes, and eliminate backlogs. And, separate from implementation of the specific provision of the FDA Modernization Act relating to use of voluntary consensus standards in the device review process, FDA has asked questions that solicit suggestions from stakeholders. Specifically, the Agency has asked:

- *How can FDA work with its partners to ensure that products -- domestic and foreign -- produced and marketed by the regulated industry are of high quality and provide necessary consumer protection; and how can FDA best establish and sustain an effective, timely, and science-based postmarketing surveillance system for reporting, monitoring, evaluating, and correcting problems associated with use/consumption of FDA-regulated products?*

- *What approach should FDA use to ensure an appropriate scientific infrastructure with continued access to scientific and technical expertise needed to meet its statutory obligations and strengthen its science-based decision-making process?*

- *What do you believe FDA should do to adequately meet the demands that are beginning to burden the application review process, especially for non-user fee products, so that it can meet its statutory obligations to achieve timely product reviews?*

In response, NCCLS respectfully proposes that FDA could meet its statutory obligations, access needed scientific expertise, and be responsive to the latest post-market performance information by relying on the expertise of NCCLS in FDA's review of breakpoints and quality control ranges of antimicrobial drugs.

NCCLS's Subcommittee on Antimicrobial Susceptibility Testing (see Attachment 1) is comprised of well-recognized clinical microbiology, infectious disease, and clinical pharmacology experts, including the current chair of FDA's own Antiinfective Advisory Committee. The subcommittee has a mission statement (see Attachment 2) to guide its deliberations; the values that guide this mission are quality, accuracy, fairness, timeliness, teamwork, consensus, and trust. Over the past several years, the NCCLS Subcommittee on Antimicrobial Susceptibility Testing has developed and updated a guidance document (see Attachment 3) that details the kinds of data needed to establish susceptibility testing breakpoints and quality control ranges, and an approach to organizing and presenting the data to the subcommittee. This was accomplished by a working group that included a representative from the FDA Division of Anti-Infective Drugs, representatives from the professional sector, and several representatives of the pharmaceutical industry. This document clearly stipulates the kinds of data needed by the subcommittee for decision making, and establishes uniform criteria for use by all pharmaceutical companies.

Because there is strong pressure from the healthcare community, manufacturers need to have the NCCLS subcommittee evaluate their test data and establish susceptibility breakpoints based on those data. As a further consequence, submissions are made using the methodology developed by NCCLS. This already has had a significant benefit to FDA. Manufacturers are submitting clearer and better organized data sets when they submit their data to the Agency, with the result that the review at FDA is more efficient. FDA could save still further resources if it focused its review on the clinical data to establish safety and efficacy and relied on NCCLS to establish susceptibility testing breakpoints and quality control ranges.

In many cases, NCCLS breakpoints are established before an NDA is approved by FDA --- either because the company wants to have NCCLS values established for the final phases of investigational use, or because the drug is already approved in a country in which NCCLS standards are well recognized.

In virtually all cases, the breakpoints established by FDA when it approves new drug labeling are identical to those established by NCCLS. On the other hand, there are some differences. The NCCLS subcommittee has the ability to assess and respond to current trends in emerging resistance. Increasingly in the United States and the rest of the world, physicians are required to deal with common infectious agents that have newly acquired resistance to an antimicrobial agent routinely used to treat them. It is imperative that new information about emerging resistance from clinical microbiologists and infectious disease specialists, whether from CDC or elsewhere, whether in this country or abroad, be assessed as soon as possible and disseminated to the clinical testing community. Included in the subcommittee's mission statement is the goal to "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." This has been manifest in revised NCCLS susceptibility interpretive criteria for the detection of drug-resistant *Enterococcus* species, resistance due to the production of extended-spectrum beta-lactamase enzymes by some common gram-negative bacteria, and oxacillin-resistance in coagulase-negative *Staphylococcus* species. Breakpoints have also recently been modified to facilitate the detection of vancomycin resistance in staphylococci, should the trend of decreasing susceptibility to that agent continue during the next several years.

The dynamic NCCLS standards-development process has provided critical updates for detection of the emerging antimicrobial resistance mechanisms that have been noted during the past several years. For example, NCCLS first published revised interpretive criteria for the extended-spectrum cephalosporins when tested against *S. pneumoniae* following recognition the previous year of clinical failures (deaths) due to meningitis caused by strains with newly acquired resistance to those drugs. These revised breakpoints have been widely adopted by clinical microbiology laboratories and endorsed by public health agencies and professional

societies. There has not been a mechanism in place whereby FDA could respond to such developments by changing the FDA breakpoints included in the approved product package insert.

Facing dwindling resources with which to fulfill its statutory obligations, FDA has asked for innovative solutions that would accomplish the equivalent level of public health assurance. FDA adoption of NCCLS antimicrobial susceptibility breakpoints for use in drug labeling is just such a solution. It would reduce the burden on FDA in the NDA process, allowing resources to be used in other areas. It would allow FDA to assert that it is assuring access to the latest information on emerging drug resistance. It retains critical responsibility for clinical evaluations of safety and efficacy of individual antiinfective drugs at FDA. The opportunity exists for FDA to apprise the NCCLS subcommittee of any clinical concerns that may warrant reconsideration of particular data and possible revision of breakpoints.

FDA adoption of NCCLS antimicrobial susceptibility breakpoints for use in drug labeling would have all of these benefits while providing full FDA participation in the scientific deliberations of the NCCLS subcommittee. As far back as anyone can remember, an FDA scientist has participated in this subcommittee as a voting member, able to voice concerns or suggest alternate interpretation of data as needed. Against the remote possibility that the decision of the NCCLS subcommittee is to adopt a breakpoint with which FDA cannot agree, FDA retains the authority to preclude its use in drug labeling (as is the case now with the HHS Secretary having the authority, seldom if ever used, of intervening in implementation of specific standards in USP monographs).

FDA may also wish to take advantage of new NCCLS activities under the Subcommittees on Antifungal Susceptibility Tests (Attachment 4) and Veterinary Antimicrobial Susceptibility Testing (Attachment 5). In a fashion parallel to that for human antimicrobial drugs, NCCLS is in the process of developing methodology and breakpoints that could be adopted by FDA. Similar activities are underway in antimycobacterial and antiviral susceptibility testing.

NCCLS is prepared to further discuss these ideas with the Agency, with the goal of establishing a mechanism by which NCCLS would continue to work to establish antimicrobial susceptibility breakpoints, and those values would be adopted by FDA. We would argue that there is value to including other stakeholders, such as pharmaceutical manufacturers and the infectious disease community, in these discussions.

Respectfully submitted,

John V. Bergen, Ph.D.
Executive Director

JVB/dlc

Attachment 1 - Roster of the Subcommittee on Antimicrobial Susceptibility Testing members and advisors
Attachment 2 - Subcommittee on Antimicrobial Susceptibility Testing mission statement
Attachment 3 - NCCLS publication M23-T3
Attachment 4 - Roster of the Subcommittee on Antifungal Susceptibility Tests members and advisors
Attachment 5 - Roster of the Subcommittee on Veterinary Antimicrobial Susceptibility Testing members and advisors

Attachment 1

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Attachment 2

NCCLS Subcommittee on Antimicrobial Susceptibility Testing Mission Statement

The NCCLS 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 NCCLS voluntary consensus process, the subcommittee develops standards that promote accurate antimicrobial susceptibility testing and appropriate reporting.

The mission of the NCCLS 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 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.
- 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 NCCLS guidelines. The values that guide this mission are quality, accuracy, fairness, timeliness, teamwork, consensus, and trust.

Attachment 3

M23-T3
Vol. 18 No. 5
Replaces M23-A
Vol. 14 No. 9

April 1998

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

PLEASE

This tentative document is published for trial application and field evaluation as the second step in the NCCLS consensus-review process. Please send comments on scope, approach, and technical and editorial content to the Executive Offices.

Comment period ends
2 November 1998

The subcommittee responsible for this document will assess all comments received by the end of the comment period. Based on this assessment, a new version of the document will be issued. Readers are encouraged to send their comments to the NCCLS Executive Offices, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898; Fax: (610) 688-0700, or to the following e-mail address:

standard@nccls.org

COMMENT

This document addresses the required and recommended data needed for the selection of appropriate interpretative standards and quality control guidelines for new antimicrobial agents.

NCCLS

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

Abstract

This document offers guidance for developing data on antimicrobial susceptibility testing of aerobic and anaerobic bacteria; data developed according to this guideline will be used in establishing interpretive and quality control criteria for NCCLS antimicrobial susceptibility testing standards. Human pharmacokinetics, in vitro drug characteristics, distributions of microorganisms, and correlation of test results with outcome statistics are addressed from the perspective of interpretation of test results. In addition, the document addresses clinical confirmation of interpretive criteria and quality control limits. For clinical confirmation, the "ideal" data set may not be obtained during development of a new drug. Users of this guideline should understand the limitations and work together toward the best educated conclusions.

(NCCLS. *Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters; Tentative Guideline—Third Edition.* NCCLS document M23-T3 [ISBN 1-56238-347-7]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 1998.)

THE NCCLS consensus process, which is the mechanism for moving a document through two or more levels of review by the healthcare community, is an ongoing process. Users should expect revised editions of any given document. Because rapid changes in technology may affect the procedures, methods, and protocols in a standard or guideline, users should replace outdated editions with the current editions of NCCLS documents. Current editions are listed in the *NCCLS Catalog*, which is distributed to member organizations, and to nonmembers on request. If your organization is not a member and would like to become one, and to request a copy of the *NCCLS Catalog*, contact the NCCLS Executive Offices. Telephone: 610.688.0100; Fax: 610.688.0700; E-Mail: exoffice@nccls.org.

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

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WORKING GROUP ON DEVELOPMENT OF IN VITRO SUSCEPTIBILITY TESTING CRITERIA AND QUALITY CONTROL PARAMETERS

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Foreword

NCCLS is responsible for the development of standard in vitro tests for measuring the susceptibility of bacteria to antimicrobial agents. In this regard, the NCCLS Subcommittee on Antimicrobial Susceptibility Testing is responsible for developing and updating the following susceptibility testing standards:

M2-A6 *Performance Standards for Antimicrobial Disk Susceptibility Tests–Sixth Edition; Approved Standard*

M7-A4 *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically–Fourth Edition; Approved Standard*

M11-A4 *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria–Fourth Edition; Approved Standard.*

M23-T3 provides guidance on the types of data that are useful to and/or required by the subcommittee when determining interpretive criteria and quality control limits for inclusion in the above noted documents. It also provides guidance both for new antimicrobial agents that are about to be made available for clinical use, as well as for marketed antimicrobial agents that require subsequent reassessment.

All sections of the guideline preceded by an asterisk (*) describe information required for review by the subcommittee. All other sections describe recommended information.

The previous edition of this document (M23-A) proved to be a needed and well received starting point in defining the types of information necessary to assist the subcommittee in determining interpretive criteria and quality control limits. This edition builds upon M23-A, providing more complete guidance in numerous areas (i.e. Pharmacokinetics/Pharmacodynamics and Clinical Correlations). In addition, sections have been added to address the following topics: acceptability of both U.S. and non-U.S. data; use of data derived from previously accepted reference methods; resolution of differences between the NCCLS and regulatory agencies. The entire section on quality control limits has been revised following a thorough review of varying approaches to determine such limits. Wording has been added to minimize the possibility of creating unfair advantages or disadvantages for one antimicrobial relative to another. For example, this document states "when a reassessment is considered that could potentially impact and/or apply to other similar products, then all products so affected should be considered at the same time." This edition also clearly defines circumstances when a reassessment of interpretive criteria or QC parameters can be considered. When such reassessments are made, the guidelines outlined in this document are to be followed, and the data upon which the original decision was made are to be considered.

The working group was interested in modifying the section concerning error rates; however, it was felt that more data would be needed in order to accomplish this. This issue will be further evaluated, and the working group needs your insight and suggestions.

The M23 guideline is a key foundation document for NCCLS's widely used "family" of susceptibility testing documents. It is intended to offer direction and guidance for developing data on antimicrobial susceptibility testing of aerobic and anaerobic bacteria; data developed according to M23 are used by the Subcommittee on Antimicrobial Susceptibility Testing as the basis for establishing interpretive and quality control criteria for NCCLS's antimicrobial susceptibility testing standards. The intent is to ensure that a "level playing field" is maintained, independent of manufacturer, health care professional, or government agency, in data presentation to the subcommittee and in subcommittee determinations based on those data.

M23-T3 is a revision of M23-A, the previous approved version. The subcommittee has recommended issuing the revised edition at the tentative level in order to gain further comment input based on user experience and familiarity with the revised protocols. Comments from manufacturers and other users are essential in assuring the utility of this critical guideline.

Foreword (Continued)

M23-T3 is officially open for comment for six months (until 2 November 1998) after which the Subcommittee on Antimicrobial Susceptibility Testing will advance the guideline to a new approved edition.

In addition to the members of the working group, I wish to express my personal gratitude for the work contributed by the following persons in making this document what it is: Patricia Charache, Mary Jane Ferraro, Peter Fuchs, William Gregory, Judith Johnston, James Jorgensen, Harriette Nadler, William Novick, James Poupard, Raymond Testa, and Lauri Thrupp.

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Key Words

Susceptibility testing; antimicrobial agents; standard disk diffusion test; standard dilution methods for bacteria that grow aerobically; standard reference method for anaerobes.

NCCLS Subcommittee on Antimicrobial Susceptibility Testing Mission Statement

The NCCLS 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 NCCLS voluntary consensus process, the subcommittee develops standards that promote accurate antimicrobial susceptibility testing and appropriate reporting.

The mission of the NCCLS 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 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
- 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 NCCLS 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; Tentative Guideline—Third Edition

1 General Considerations and Time Sequence

1.1 Subcommittee Requirements

Guidelines for interpretative breakpoints and quality control (QC) limits are established by the Subcommittee on Antimicrobial Susceptibility Testing after the review of extensive data. This guideline describes the data needed for such determinations.

All sections of the guideline preceded by an asterisk (*) describe the minimum information required for review by the subcommittee. All other sections describe information that may be helpful in supporting the establishment of interpretative criteria and QC limits.

Guidelines presented in this document apply only to NCCLS documents. The guidelines do not apply to topical antibiotics.

Any reassessment (Section 1.6) of existing drugs should also follow the guidelines presented in this document whenever possible.

1.2 Time Sequence for Presentation

To ensure a successful evaluation of a new drug or new data, each sponsor (company or individual) should review the guidelines for time sequence (Section 1.2) and for presentation (Section 1.3).

- The data on quality control parameters for disk diffusion and dilution tests may be evaluated by the subcommittee any time they become available.

- The information on zone size, MIC relationships, pharmacokinetics/pharmacodynamics may be made available to the subcommittee early in the development of a drug (Phase I or II). This can assist in the selection of "provisional" breakpoints to be used by clinical investigators (Phases II and III). "Provisional" breakpoints will not be published in NCCLS documents.

- Just before, or as soon as feasible after the New Drug Application (NDA) is submitted, all requested data defined in these guidelines (including previously presented data) should be formally presented to the subcommittee for selection of interpretive criteria and QC ranges. If QC limits have already been established, it is not necessary to present these data again.

- A drug's placement in Table 1 of NCCLS documents M2 and M7 requires an FDA-approved clinical indication for the specific organism(s) under which the drug is to be listed. Alternatively, placement in Table 1 without an FDA-approved indication may be made if a public health need requires such an action. FDA-approved clinical indications are not required for a drug's placement in any other tables.

- The subcommittee may reassess the need for altering interpretive criteria or QC parameters at any time (Section 1.6). Additional supportive data may be submitted to the subcommittee from any source whenever a change appears to be necessary.

1.3 Presentation

Individuals or sponsors who wish to present data to the subcommittee must have a hard copy of their presentation (including supportive data and recommended actions) included in the agenda book for the

subcommittee meeting. Submissions should be sent to the NCCLS National Office. Agenda priority will be given for the final formal presentation of new drugs to be included in M2, M7, and M11.

1.4 Acceptability of Data

Data generated from within or from outside of the U.S. must meet the same high standards. For microbiologic data, NCCLS reference methods are to be used and so documented, including proper quality control tests. If NCCLS methods are not used, then sufficient data must be available to demonstrate the comparability of such methods to NCCLS reference methods. The design and evaluation of clinical studies should optimally conform to the most recent guidelines from the FDA or the Infectious Diseases Society of America. Data from the U.S. and from different countries or regions should be presented separately, but may be presented concurrently if comparability of such data can be established. Differences between data from the U.S. and from different countries or regions should be noted—for example, distribution of organisms, resistance mechanisms, incidence of resistance, dosages used in studies, etc.

1.5 Use of Data Derived from Previously Accepted Reference Methods

If NCCLS reference methods change, or if new reference methods are created, data from previously accepted methods will be acceptable for consideration if the relationship between the methods is known or can be demonstrated. Studies initiated after NCCLS publication of modified or new reference methods should use the modified or new method.

1.6 Reassessment of Interpretive Criteria or QC Parameters

Reassessment of Interpretive Criteria or QC Parameters may become necessary as new information becomes available. Reassessment should only be considered when there is adequate information for making a decision or when there becomes a public health need requiring action with limited clinical information. The following represents situations under which a reassessment can be considered.

- When less susceptible and/or resistant strains develop to an antimicrobial agent whose breakpoints were determined when only susceptible strains were available.
- When organisms with new mechanisms of resistance are not reliably detected using current breakpoints.
- When new dosages or formulations of an antimicrobial agent and/or new clinical usage require(s) a change.
- When new clinical and/or pharmacologic data suggest a need for reassessment.
- When actions and or data from the FDA or other regulatory authorities, College of American Pathologists, or other sources suggest the need for reassessment.
- When NCCLS approved reference methods change and such changes will have an impact on interpretive criteria and/or QC parameters.
- When other in vitro testing data suggest the need for reassessment.

When a reassessment is made, the guidelines presented in this document are to be followed to the extent possible. The data upon which the original decision was made should also be considered in any reassessment.

If the manufacturer submits a request to the FDA for revisions in interpretive breakpoints or QC limits, they are encouraged to submit such data for consideration by the subcommittee.

If the need for reassessment is brought from a source other than the manufacturer of the product, then the manufacturer must be notified that a reassessment is being considered. This notice must allow reasonable time for the manufacturer to prepare a packet of relevant data for incorporation into the meeting agenda book, if the manufacturer so desires.

When a reassessment is considered that could potentially impact and/or apply to other similar products, then all products so affected should be considered at the same time. In such instances, NCCLS will formally notify all subcommittee members and advisors, and all manufacturers whose drugs could be impacted by such a reassessment. This notice must allow reasonable time for the preparation of relevant data for incorporation into the meeting agenda book.

When a change is made with limited information or when the guidelines outlined in this document are not followed due to a pressing public health need, this should be so noted within the document.

2 Data for Determining Susceptibility Test Breakpoints

2.1 In Vitro Drug Characteristics

*Data on the stability of appropriate concentrations of the drug at incubation and storage temperatures specified for NCCLS dilution methods (M7 and M11) must be provided.

*Data on the preparation of stock solutions, including diluent and solvent information, must be presented for inclusion in Table 4 of Document M7.

*Because different methods could be used to describe MIC endpoints, data showing the relationship or comparability of these endpoints for a relevant subset of representative organisms for NCCLS standard (i.e., broth and agar) methods and media should be presented.

2.2 Distribution of Microorganisms

*Dilution and disk diffusion tests should be done on at least 500 isolates according to NCCLS methods and should contain examples of clinically relevant isolates appropriate both for the class of compound being evaluated and for the anticipated clinical use of the compound. They should also include isolates showing important resistance mechanisms. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci should be included in the evaluation of antistaphylococcal agents.

*The MIC/zone diameter distribution used for the in vitro test development should be compared with those obtained from a large geographically diverse representative survey of recent clinical isolates.

2.3 Pharmacokinetics/Pharmacodynamics

*An analysis that examines the relation between pharmacokinetic/pharmacodynamic parameters and efficacy should be included. This analysis might include (but not be limited to) the following: time serum or plasma levels that exceed the MIC; peak serum or plasma level: MIC ratio; and area-under the serum drug concentration (AUC):MIC ratio. Data for this analysis might be derived from experimental models of infection, comparison of MICs with serum levels in humans following proposed dosage regimens, or even results from clinical studies. If such data are not available, data on the postantibiotic effect and impact of increasing drug concentrations on bacterial killing may be helpful.

*The pharmacokinetic/pharmacodynamic parameters of interest should be calculated for aerobic and fastidious organisms for which breakpoints are sought. The serum concentrations resulting from proposed dosage regimens in humans should be used. Similar calculations for related drugs of the same class should be presented.

In order to assist the subcommittee in making a timely decision, the following points should be considered when putting together the pharmacokinetics/pharmacodynamics data package.

Methods for measurement of drug concentrations in serum and body fluids should be provided. If bioassay and other analytical methods (e.g., HPLC) for drug level measurement are available, the relative performance of the assays and comparisons between bioassay and other methods should be provided.

*Actual plots of serum or plasma levels in humans over time following the expected method of administration should be provided. If available, data from target patient populations should be presented. The number of subjects or patients, characteristics, and the intra- and interindividual variability of measurements should be included.

*The pharmacokinetic parameters useful for simulation, calculation of pharmacokinetic/pharmacodynamic relationships, and comparisons with existing agents of a class should be provided. The parameters included should include AUC, bioavailability, volume of distribution, clearance, and elimination half-life. The number of subjects in any study should be governed by good statistical approaches.

*Data concerning the effects of protein binding on MIC and pharmacokinetic/pharmacodynamic parameters should be included.

*Data on the metabolism and excretion of the drug in humans should be presented. If metabolized, the microbiological activity of the metabolites should be provided. If a drug is to be used for urinary tract infections, data showing the kinetics of the drug in urine should be provided. The effect of pH and cations on antimicrobial activity in urine should also be included.

Concentrations in cerebrospinal fluid must be presented if the drug will be used for treatment of meningitis. Tissue, body fluid, and intracellular concentrations of the drug may be presented.

Where data are available, it is helpful to present data on differences in AUC, expected peak and trough serum concentrations, and pharmacokinetic/pharmacodynamic parameters (e.g., AUC:proposed MIC breakpoint ratio) with anticipated dosage regimens. While data in normal human subjects are generally available, data in special target patient populations which might include children, the elderly, and populations where special dosage adjustments will be made (e.g., renal or hepatic impairment) are desirable.

2.4* Correlation of Test Results with Clinical Outcomes Statistics

During the clinical evaluation of antimicrobial agents, in vitro susceptibility (dilution or disk diffusion) test results should be correlated with therapeutic outcome. For assignment of interpretive criteria for both MICs and zone sizes, therapeutic outcome results based on both methods should be presented. This does not mean that both tests must be performed on isolates from all patients.

The clinical cure and bacteriological eradication rates should be correlated with appropriate in vitro test results to confirm the validity of the proposed interpretive criteria. There may be occasions when a clear breakpoint can be determined from the clinical data, however, due to the inherent difficulties and variabilities encountered in clinical studies this will frequently not be the case. In these situations, the clinical data will serve more to support other types of data (microbiologic and pharmacokinetic/pharmacodynamic) in determining interpretive criteria.

In the course of the development of an antimicrobial agent, the manufacturer will conduct clinical studies that will yield a large volume of data. The manufacturer should provide the subcommittee, in a summarized fashion, all relevant data needed to make breakpoint determinations. If such data have already been submitted, or will be submitted in the near future to the FDA for review, the manufacturer

should note if the data being presented are in any way different from that submitted, or to be submitted to the FDA. If the data are different, such differences should be so noted, as well as the reasons for such differences. Optimally, the design and evaluation of clinical studies should conform to the most recent guidelines from the FDA or the Infectious Diseases Society of America. In order to assist the subcommittee in making a timely decision, the following points should be considered when putting together the data package.

- A clear description of the clinical protocol(s) used should be given. This should include:
  - description of the population studied;
  - study specific inclusion/exclusion criteria;
  - dosage and duration of study and comparative drug therapies;
  - times of initial, on therapy and follow-up microbiologic and clinical assessments,
  - visits and test of cure;
  - evaluability criteria; and
  - definitions of "clinical" and "bacteriological" response.
- When the category of "improved" is used as a clinical outcome, this should be clearly defined.
- If adjunctive therapy is permitted, this should be so stated.
- If patients are permitted to switch from study antimicrobial to another (i.e. parenteral to oral switch), this should be so stated and criteria for such a change should be clearly defined.
- If surgical procedures are part of the routine care of an infection type, details concerning such procedures within the study should be discussed.

All clinical data relevant to breakpoint analysis, including an analysis of evaluable cases AND an intent to treat analysis of microbiologically documented cases should be presented. In addition, summary results for the comparative arms should be presented by individual study to assist the subcommittee in evaluation of the data. To allow optimal evaluation, clinical data must be presented separately for sites and types of infection in accordance with FDA categories, e.g., urinary tract infection (complicated and uncomplicated), pneumonia (community acquired and nosocomial), etc. In addition, subsets of patients with bacteremia should be presented.

The data analysis should be based on responses at the "test of cure" AND at the subsequent long-term follow-up visits. All "failures" should be carried forward to subsequent evaluations.

The data presented must be relevant for the anticipated use of the antimicrobial agent in clinical practice. In addition, the organisms presented should be relevant for the site of infection being studied.

All clinical and/or bacteriological failures should be presented separately according to the infecting bacteria, MIC and/or zone of inhibition, and site of infection.
In vitro data should be presented as actual MIC or zone diameter of inhibition, not simply susceptible or resistant. Quality control data should be generated and recorded for all clinical isolate susceptibility determinations (MIC and zone of inhibition).

For bacterial species that are relevant for the anticipated use of the drug, data should be presented by individual zone diameter of inhibition and/or MIC.

Infections due to single or predominant pathogens should be presented separately from true polymicrobial infections.

Data should be presented for both clinical (cure, improved, failure) and bacterial responses. When the category of "improved" is used, clinical response data should be broken down into "cure," "improved," and "failure" as separate categories. Bacteriological response data should be presented with and without "presumed" outcomes included. In addition, data should be presented for *each* MIC and for all zone diameters relevant to those MICs.

Information about species that are resistant or that have MIC or zones of inhibition near the breakpoints is of particular interest and should be presented. This data should be presented for both evaluable and intent-to-treat populations.

3 Disk Diffusion Test Methods (M2)

3.1 Disk Content Studies

In most cases, the content of the antimicrobial disk will be the same as that for other established antimicrobials that are structurally related. This generalization does not apply if the new antimicrobial represents a new class of antimicrobial agents, or exhibits different physico-chemical characterisitics, or if the MIC breakpoints or human pharmacokinetics are substantially different from those of related antimicrobials.

If necessary, preliminary studies may be carried out to determine the antimicrobial content in the disk that should be evaluated more thoroughly. The ideal disk content is one that provides zone diameters greater than 15 mm and less than 45 mm with most susceptible strains but only small zone diameters of inhibition (or no detectable zone diameters of inhibition) with resistant strains. However, susceptible breakpoint(s) should, ideally, be between 15 and 25 mm.

*When an antimicrobial disk is developed for a drug that is a combination product (e.g. beta-lactam/beta-lactamase inhibitor, trimethoprim/sulfa, etc.) then a justification for the selected ratio of the components of the disk must be presented.

3.2 Evaluation of Disk Diffusion Susceptibility Tests

3.2.1* Selection of Isolates

3.2.1.1* Sample Size

In general, studies should be performed with at least 500 isolates representing all species that are likely to be tested by the disk diffusion procedure; the majority of which should belong to clinically relevant species.

3.2.1.2* Single Species or Genus Sample Size

When interpretive criteria are being developed for those organisms or groups of organisms that have separate interpretive criteria (e.g., *Haemophilus* spp. or *Neisseria gonorrhoeae*), fewer isolates can be used. However, those isolates should represent susceptible and resistant (if recognized) clinical strains that are relevant to the antimicrobial agent being studied. A total of 100 to 300 isolates will usually suffice.

3.2.1.3* Regression Analysis

For regression analysis, all clinically relevant species should be represented, but efforts must be made to provide a reasonably even distribution of MICs over the range of concentrations tested, particularly in the range near the proposed susceptibility threshold. Such an even distribution of MICs may not be possible for some drugs and, in that case, error rate bounding may be a preferred statistic and regression statistics should not be calculated.

3.2.1.4* Error Rate Bounding

For error rate bounding, the nature of the culture collection studied is critically important. When reporting the results of such studies, the type of culture collection used must be specified. Three types of culture collections are listed below. At least one of these must be evaluated. Ideally, data generated by culture collections (1) and (2) should be available for review by the subcommittee.

(1) A carefully selected challenge set of microorganisms may be gathered to include isolates with all known resistance mechanisms that may be relevant to the type of antimicrobial agent that is being evaluated. A similar number of susceptible isolates with no known resistance mechanisms should be included in such a challenge set of isolates and all relevant species should be represented.

(2) A large collection of isolates (over 2,000) may be gathered from several geographically separate institutions to represent consecutively isolated strains that are normally subjected to susceptibility tests. Except for antimicrobials being developed for limited indications, no more than 20 to 30% of these isolates will be of the same species. In this type of collection, the more common species will predominate and resistant isolates will be included as they are being encountered in the institutions contributing isolates.

(3) A randomly selected collection of stock cultures can be gathered to represent all relevant bacterial species without prior knowledge of the study drug's activity. With many broad spectrum antimicrobial agents, few resistant isolates are likely to be included in this type of culture collection.

3.2.2* Commercially Prepared Reagent Disks

Attempts should be made to conduct the initial studies with commercially prepared reagent disks (minimum potency of 100%) and media. If that is not done, analysis of laboratory-prepared disks should be confirmed with commercially produced disks when these reagents are available.

3.2.3* Regression Line Determination

Statistical analysis of these data may involve the calculation of a regression line correlating MICs and zone diameters of inhibition. Calculations must exclude undefined measurements (such as no zone of inhibition or off-scale MICs). To evaluate the linear portion of the parabolic regression curve, the regression statistics may be recalculated using only isolates with MICs two to three dilutions above and below the proposed MIC breakpoint. In either case, all data should be presented as scattergrams, including the end points that were excluded when calculating the regression line.

3.2.4* Error Rate-Bounded Method

3.2.4.1* Interpretive Criteria and Discrepancy Rates

The error rate-bounding method of Metzler and DeHaan[1] may be used to select zone-size interpretive criteria and to calculate interpretive discrepancy rates. The Metzler and DeHaan method usually needs to be modified[2] because two MIC breakpoints are normally described to define an "Intermediate" category.[4,5] Data should be displayed as a scattergram with zone diameters on the x-axis and MICs on the y-axis, and with horizontal and vertical lines showing the proposed interpretive breakpoints.

3.2.4.2* Acceptable Error Rates

In practice, the proposed zone-size breakpoints are simply adjusted until the number of false-susceptible disk diffusion test results (very major errors) and false-resistant disk tests (major errors) are held to a minimum. Ideally, when evaluating a large collection of unselected clinical isolates, very major error rates should be less than 1.5% and major errors should occur with less than 3% of all isolates.

3.2.4.3* Major and Very Major Error Rates

Because very major errors can only occur with isolates that are resistant by the dilution method, very major error rates should be calculated using the number of resistant strains as the denominator rather than the total number of isolates tested. For the same reason, major error rates should be calculated by using the total number of susceptible isolates as the denominator. Both types of error rates should be presented: one calculated by using the restricted number of isolates as a denominator and the other using the total number of isolates tested. However, historically the acceptable error rates that are described in Section 3.2.4.2 were based on the total number of consecutive isolates that were evaluated and not with a more biased collection of challenge strains or by restricting the number of isolates in the denominator. If error rates are calculated for a restricted population of isolates, greater error rates will generally result.

3.2.4.4* Comprehensive Tabulation

A separate tabulation should be provided showing the total number of isolates for each species tested and the number of minor, major, or very major errors that were recorded for each species.

3.2.5* Final Selection of Breakpoints

The final selection of breakpoints must include evaluation of pharmacokinetics, regression line analysis, overall error rates, and clinical verification of breakpoints by clinical and bacteriological response rates.

3.2.6* Cross-Resistance and Cross-Susceptibility Studies

Cross-resistance and cross-susceptibility studies should be conducted by dilution and disk diffusion tests using available drugs in the same class. These studies should be done with 300 or more representative clinical isolates. When possible, representative isolates of uncommonly encountered organisms should also be included. Tables showing results with different species should be presented.

4 Dilution Test Methods for Aerobic Bacteria (M7)

The MICs may be determined by approved methods to establish parity of results.

*Comparisons of broth microdilution and agar dilution MICs should be done on 100 or more clinical isolates (on scale) with a distribution similar to that described in Section 3.2.1.

*When an antimicrobial is developed that is a combination product (e.g., beta-lactam/beta-lactamase inhibitor, trimethoprim/sulfa, etc.) then a justification for the selected ratio(s) of the various components to be used in dilution test methods must be presented.

5 Anaerobe Susceptibility Tests

If the spectrum of the new drug includes anaerobic bacteria, intermethod comparisons may be made of results obtained with one or more of the alternative methods to the agar dilution reference method (see NCCLS document M11). These studies should contain a reasonable number (300 or more) of clinically relevant isolates. Results should be reported for broth microdilution versus agar dilution.

6 Quality Control Limits

6.1 Preliminary QC Testing

During the drug development process, testing of NCCLS-recommended QC strains should be performed to establish preliminary QC limits and to determine the impact of procedural variations on test performance. Testing should be performed using all appropriate NCCLS methods to establish

equivalency of methods (e.g., agar dilution and broth microdilution). Testing may be done at one laboratory.

If this preliminary testing is not done, future QC development testing should include all testing methods for which a QC limit is desired.

6.2 Disk Diffusion Tests (M2)

* To monitor the performances of in vitro disk diffusion susceptibility tests, it is necessary to know the limits of acceptable variability in zone sizes using appropriate QC strains. These strains should be standard strains from a recognized source [e.g., the American Type Culture Collection (ATCC)]. All NCCLS-recommended QC organisms appropriate for the drug should be evaluated.

To establish QC limits for disk diffusion tests, acceptable results from the laboratories of at least seven separate and distinct institutions should be analyzed. The evaluation should involve two lots of disks from two different manufacturers if possible.

Three lots of Mueller-Hinton agar (MHA) from different manufacturers (see the most current version of NCCLS document *M6—Protocols for Evaluating Dehydrated Mueller-Hinton Agar)* should be used. Each laboratory should use each MHA lot. Each lot should meet the M6 performance requirements. Ideally, at least 95% of values should be included in the proposed range.

At least seven laboratories should test each QC strain on each MHA lot and each disk lot for ten days. This results in 70 data points for each individual MHA and disk lot and 420 total data points. The same principles should be used when other media are required (e.g., fastidious organisms [see NCCLS documents M2, M6, and M7]).

A control drug of similar class as the study drug should also be tested. The results for the control drug must be within the expected control limits each day of testing. If this is not the case, an investigation as to the cause of the problem should be conducted and the day's testing should be repeated.

The results from all laboratories must be presented. Results for both the study drug and the control drug should be presented as a distribution of zone diameters of inhibition by each QC strain for each laboratory and MHA lot. Statistical methods (e.g., Gavan et al [3]) should also be used.

6.3 Dilution Tests for Aerobic and Fastidious Organisms (M7) and Anaerobic Bacteria (M11)

*For purposes of susceptibility testing, fastidious organisms are defined as those that will not grow satisfactorily in (or on) unsupplemented Mueller-Hinton (MH) medium within 24 hours.

To monitor the performance of in vitro dilution tests, it is necessary to establish the limits of acceptable variability in MICs using appropriate QC strains. These strains should be standard strains taken from a recognized source (e.g., ATCC). All NCCLS-recommended QC strains appropriate for the study drug should be evaluated.

To establish QC limits for dilution tests, acceptable results from at least seven laboratories from seven separate and distinct institutions should be analyzed. Three lots of MH broth, each from a different manufacturer, should be used. Each laboratory should use each MHB lot. Ideally, at least 95% of the values should be included in the proposed range and will include mode ± 1 log. Whenever possible the low end of the QC range should include dilutions which can be "accurately" prepared (i.e., dilutions lower then 0.03 mcg/ml should be avoided) or more than five dilutions below the drugs' susceptibility breakpoint.

Each of the seven laboratories should test each QC strain on each media lot for ten days. This results in 70 data points for each individual media lot and 210 total data points. The same principles should

be used when other media are required (e.g., fastidious organisms [see NCCLS documents M2, M6, M7]).

A control drug of similar class as the drug under development should also be tested. The results for the control drug must be within the expected control limits each day of testing. If this is not the case, an investigation as to the cause of the problem should be conducted and the day's testing should be repeated.

For each study drug and control drug, a twofold dilution schedule should be used to provide on-scale end points for all determinations.

The results from all laboratories must be presented. The results for both the study drug and control drug should be presented as MIC distributions for each lot of media, for each laboratory, and for all data points combined.

Additionally, the results of the testing to establish the equivalency of methods should be presented. In the absence of equivalency data, the accepted QC limits will be noted to apply only to the method used to obtain the data.

7 Resolving Differences Between NCCLS and Regulatory Authorities

Minimum inhibitory concentration (MIC) and zone diameter breakpoints, and quality control limits are established by the Subcommittee on Antimicrobial Susceptibility Testing after review of extensive data. Numerous regulatory agencies independently establish interpretative criteria and quality control limits based on evaluation of extensive data submitted by pharmaceutical manufacturers. This independent process can at times produce interpretations that are discrepant. Every effort should be made to minimize or resolve such discrepancies. When the subcommittee makes a change that will result in a discrepancy, the manufacturer of the product will be encouraged to submit the data upon which the change is made to the appropriate regulatory authority, and/or request additional analysis or reassessment by the subcommittee.

References

1. Metzler DM, DeHaan RM. Susceptibility tests of anaerobic bacteria: Statistical and clinical considerations. *J Infect Dis.* 1974;130:588–594.

2. Brunden MN, Zurenko GE, Kapik B. Modification of the error-bounded classification scheme for use with two MIC breakpoints. *Diagn Microbiol Inf Dis.* 1992;15:135–140.

3. Gavan TL, et al. Quality control limits for ampicillin, carbenicillin, mezlocillin, and piperacillin disk diffusion susceptibility tests: A collaborative study. *J Clin Microbiol.* 1981;14:67–72.

Summary of Comments and Committee Responses

M23-A: Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters; Approved Guideline

Section 3.2.2

1. The statement "minimum potency of greater than 100%" does not make sense. How can there be anything with a potency of greater than 100%? Shouldn't this be listed simply as potency of 100%?

- **Antibiotic disks are commonly manufactured with a final potency of greater than 100%. Over time, storage of the disks before use can lead to deterioration of the antibiotic. This deterioration may result in potency levels lower than that originally measured in the disk.**

Related NCCLS Publications*

M2-A6 **Performance Standards For Antimicrobial Disk Susceptibility Tests—Sixth Edition; Approved Standard (1997).** Current recommended techniques for disk susceptibility testing, new frequency criteria for quality control testing, and updated tables for interpretive zone diameters are provided.

M6-A **Protocols For Evaluating Dehydrated Mueller-Hinton Agar; Approved Standard (1996).** The document discusses a protocol for the development of primary and secondary reference lots of disk diffusion susceptibility testing medium.

M7-A4 **Methods For Dilution Antimicrobial Susceptibility Tests For Bacteria That Grow Aerobically—Fourth Edition; Approved Standard (1997).** The document discusses reference methods for the determination of minimum inhibitory concentration (MIC) of antimicrobial agents with bacteria that grow aerobically, as well as broth macrodilution, broth microdilution, and agar dilution methods.

M11-A4 **Methods For Antimicrobial Susceptibility Testing of Anaerobic Bacteria—Fourth Edition; Approved Standard (1997).** The methods for susceptibility testing of anaerobic bacteria; a description of a reference agar dilution method and alternative agar methods (Wadsworth and limited dilutions); broth microdilution and broth (macro) dilution procedures; and quality control criteria for each procedure are discussed.

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* Proposed- and tentative-level documents are being advanced through the NCCLS consensus process; therefore, readers should refer to the most recent editions.

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