BD Biosciences
Post Office Box 999
Sparks, Maryland 21152-0999
tel: 410.316.4000
www.bd.com

0149 '00 JUN -7 09:10

BD
Indispensable to human health

June 6, 2000

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

RE: Docket No. 00D-0109
Draft Guidance on Review Criteria for Assessment of Antimicrobial Susceptibility Devices

Dear Sir or Madam:

These comments are submitted in response to the Food and Drug Administration's (FDA's) draft guidance entitled "Guidance on Review Criteria for Assessment of Antimicrobial Susceptibility Devices." These comments represent a collaborative effort by representatives of five manufacturers of antimicrobial susceptibility testing (AST) devices. These manufacturers include the following: **AB Biodisk; Becton, Dickinson and Company; bioMerieux, Inc.; Dade Behring Inc. (Microscan® Systems); and Trek Diagnostic Systems.** These manufacturers have been meeting via telephone and in person for nearly two years to address issues and concerns raised by the FDA Microbiology Devices Advisory Committee in February 1998 and to develop possible revisions to FDA's 1991 draft guidance document. Therefore, we very much appreciate this opportunity to provide formal comments on the proposed guidance.

We applaud FDA's efforts to update and streamline the 1991 draft guidance document. However, we have several areas of concern and believe there are alternative approaches to the assessment of AST devices that could provide valuable information to FDA, to the clinical laboratory, and to industry. We believe that a meeting with all stakeholders (the agency, representatives from the clinical laboratory community, and industry) would be an efficient way to ensure that the intentions of the Advisory Committee have been appropriately addressed. Given that NCCLS M23-A2, which covers assessment of VME and ME rates, is expected to be released early next year, this is a good time to work together on these issues. We propose that such a meeting would include key members of the NCCLS M23 Working Group who have approached the issue of error rates from both clinical and statistical perspectives.

00D-0109 C5

Our areas of concern with FDA's proposed guidance include the following:

- Assessment criteria that are more stringent than previously established criteria, including criteria for essential agreement (EA), Very Major Error (VME) rates, and absolute categorical agreement (CA), as well as requirements to apply these criteria to small subsets of data and to initial test results only, without regard for circumstances in which repeat test results may be appropriate;
- Acceptance criteria for VME rates;
- Lack of guidance regarding repeat testing;
- Assessment of challenge strain performance based only on previously established results;
- Design of the precision/bias study;
- Requirement for extensive colony count testing of inocula; and
- More stringent limitations in labeling and software.

Each of these areas of concern will be discussed in more detail below.

In addition, we have other concerns and comments that we ask you to consider. These concerns and comments, along with suggested revisions or alternative proposed language, have been incorporated directly into the draft guidance so that they follow the section being addressed (See Attachment 1). Concerns, comments, and suggested revisions are enclosed in a box to make them easier to differentiate from the draft document. Most of these were provided previously to FDA by way of a letter in October 1999 to Dr. Woody DuBois, FDA Microbiology Branch Chief, and are included here for formal submission under the notice and comment process.

* * * * * *

I. Assessment Criteria

Performance Requirements

Performance requirements for AST devices have been made more stringent in ways that we do not believe were intended by the FDA Microbiology Devices Advisory Committee. FDA's current guidance (hereafter referred to as the 1991 draft guidance) requires that EA be 90% or greater and that VME rates be less than 1.5%. The 2000 draft guidance contains additional requirements regarding 95% confidence intervals for EA and VME rates. EA must now be greater than 90% and the lower 95% confidence limit cannot be less than 90% (Section 12.1.1 and Table 6 of the 2000 draft guidance). The statistical criteria for VME acceptance now include limits for the 95% confidence interval based on the VME rate, in addition to the 1.5% rate target (Section 12.1.3 and Table 5 of the 2000 draft guidance).

The change from "≥ 90%" to "> 90%" for EA may appear to be minor; however, the simple change in sign from "≥" to ">" has effectively raised the required level of performance above what was previously acceptable. EA must now be statistically greater than 90%, where previously, EA was required not to be statistically different from 90%.

The practical effect of this change for EA is a reduction in the number of allowable discrepant results. An EA of 90/100 (90%) or 10 discrepant results would be acceptable according to the 1991 draft guidance document. With the same sample size, the 2000 draft guidance requires an EA of 96/100 (96%) and allows only four discrepant results. This is a significant reduction in the number of allowable discrepant results. We believe that the 1991 criterion that EA be 90% or greater is appropriate.

The addition of confidence interval requirements for VME rates is more stringent than the 1991 draft guidance requires. Although the 1.5% target has not changed, the 2000 draft guidance requires evidence that the VME rate is not statistically different from 1.5% and that it is statistically less than 7.5%. This effectively increases the minimum number of resistant strains required to show acceptable performance. For example, under the 1991 draft guidance, a minimum of 20 resistant strains with zero VMEs would be acceptable, while the 2000 draft guidance more than doubles the minimum number to 48 with zero VMEs. Because the topic of VME rates is so important, we have provided a detailed discussion in Section II below.

Under the 1991 draft guidance, CA has been assessed for full MIC systems using all test results ± two doubling dilutions or more from reference. The 2000 draft guidance proposes to calculate CA based on interpretation only. Given the inherent variability in dilution-based devices, we believe it is appropriate to allow ± one dilution errors to be included in the definition of CA for both MIC and breakpoint formats. Alternatively, when absolute CA falls below the 90% target and the errors are close to the interpretive breakpoints, a slightly lower CA could be deemed acceptable. This approach is similar to the one under consideration by the NCCLS AST Subcommittee Working Group on M23 for assessing VME and ME rates.

Application of Performance Requirements to Data

The 2000 draft guidance requires that results be broken out into various subsets for analysis. One subset would consist only of those microorganisms listed in the Indications for Usage (IFU) section of the approved drug labeling. Another would include organisms listed in the IFU and Microbiology sections of the approved drug labeling. The proposed guidance would also require analysis of "evaluable" results, defined in a footnote to Table 6 as those falling within the interpretive range plus and minus two dilutions. However, it appears that the same acceptance

criteria apply to all subsets, regardless of sample size. This may be unnecessarily restrictive, resulting in the loss of useful information, especially for new drugs for which only a small number of resistant organisms have been found.

Data should be presented and acceptance criteria applied to *all* strains tested. There are organisms other than those in the IFU or Microbiology sections with similar mechanisms of resistance that could provide value in the evaluation of an AST system. Data should also be evaluated with the more clinically significant organisms (e.g., the organisms in the IFU and Microbiology sections of the approved drug labeling) or by grouping organisms with similar mechanisms of resistance or characteristics. In addition, all on-scale results should be analyzed rather than limiting analysis to "evaluable" results. The proposal to limit the analysis to only those closer to the breakpoint will unnecessarily limit the number of strains evaluated.

The 2000 draft guidance also indicates that repeat test results for challenge and reproducibility strains will not be considered and, although not prohibiting repeat testing of fresh clinical isolates, provides no guidance on how this could be done and the results analyzed in a way that FDA would accept. We believe that repeat testing may be appropriate in some circumstances and that manufacturers should be allowed some flexibility. This topic is discussed in more detail in Section III below.

We believe that the acceptance criteria stated in Section 12.1 should be used as targets. If criteria are not met, a limitation should be applied unless the manufacturer can provide justification as to why the performance should be considered acceptable (e.g., EA less than 90% when lack of agreement is primarily due to two-dilution errors at very low concentrations; CA less than 90% when there are a large number of strains with MICs near the breakpoint).

We recommend that Section 12.1.1 regarding EA and CA criteria be revised as follows.

Alternative Language for Section 12.1.1

An EA or CA less than 90% may be acceptable under some circumstances. Manufacturers will be expected to discuss with FDA the rationale for accepting an EA or CA less than 90%. It may be possible to establish acceptable agreement between reference and test methods by examining the distributions of MICs at or near the breakpoints for both reference and test methods. If there is adequate statistical power and the distributions are not statistically different, then a contraindication may not be necessary. Another possibility is to apply different error rate limits based on the distance the test result is from the breakpoints.

II. Acceptance Criteria for Very Major Error (VME) Rates

FDA has proposed that statistical criteria for error rate acceptance include an upper 95% confidence limit of ≤ 7.5% for the true VME rate and a lower confidence limit of ≤ 1.5%. FDA's approach to VME rates and the use of confidence intervals merit careful consideration. However, we do not believe it fully addresses either the concerns voiced by the FDA Microbiology Devices Advisory Committee members or concerns voiced by industry. The application of these criteria to smaller and smaller data subsets is both unnecessary and unrealistic. In addition, FDA's proposal does not consider the approach, currently under review by the NCCLS AST Subcommittee Working Group on M23, to look at a range of allowable discrepancy percentages based on distance from the S and R breakpoints.

FDA Microbiology Devices Advisory Committee Concerns

The concerns with the 1991 draft guidance and VME rates voiced by the committee related to the population of resistant organisms tested and the requirement that the VME rate be no larger than a specific number (1.5%). While the issue of testing strains with newer resistance mechanisms is more fully addressed in the selection of the challenge set, it does, however, have some bearing on the VME rate issue because of the potential limitations on number of resistant strains available for testing. For example, the known population of resistant strains may be small, e.g., less than 40, making it impossible to meet the VME requirements in the proposed guidance.

The recommendation made by the FDA Microbiology Devices Advisory Committee was that an acceptable range of errors be established rather than a single value for VME. An acceptable range for errors would remove the problem of having to establish specific sample sizes for the number of strains that must be tested and would also recognize that the uncertainty in the VME rate estimated from a small (20) number of resistant strains is large. The committee also indicated that there may only be a limited number of known resistant strains and recognized that the manufacturer would have a difficult time showing statistical variation.

An additional concern was that rigid application of the 1.5% VME rate could potentially result in rejecting an otherwise reasonably good procedure. The example given was that even one error out of ten strains might still benefit public health; however, under both the 1991 and 2000 draft guidances, the procedure would be "rejected" with a limitation.

Industry Concerns

Industry is concerned that FDA's interpretation of the panel's request for a range for acceptable VME rates has produced a guidance that is more restrictive than what is currently in place. The proposed guidance has a requirement that the estimated 95% confidence interval for a VME rate fall within a range (lower confidence bound less than 1.5% and upper confidence bound less than or equal to 7.5%). While this appears to satisfy the request that an acceptable range or interval of errors be established, it is "tighter" than the 1991 draft guidance in that it forces the 95% confidence interval to fall within an acceptable range, not just the estimated VME rate. It also effectively increases the minimum number of resistant strains required to show acceptable performance. The current guidance accepts a minimum of 20 resistant strains if zero VME's are observed. The proposed guidance more than doubles the sample size to 48 resistant strains with zero VME's.

FDA may want to consider an interval along with a nominal value for VME rates. For example, the target VME could remain at 1.5% and an acceptable interval range from 0 to 7.5%. This is a different interpretation than the confidence interval requirement because it states that a VME rate as high as 7.5% would be acceptable. The developer would then have to show that the new system is not statistically different from this requirement.

Alternatively, FDA may want to consider a range of acceptable error rates relative to the S and R breakpoints in the manner being considered by NCCLS. The ranges proposed by Dr. Peter Fuchs and Bruce Craig are based on both empirical data (P. Fuchs) and computer simulations (B. Craig). These ranges can be set to be symmetric or to be more restrictive for very major discrepancies.

Additional Metric for Evaluating the Impact of VME and ME Rates

To better understand the impact of VME rates and to try to lend an objective evaluation of the proposed criteria, predictive values of sensitive and resistant test results were examined. Because the requirements in the proposed guidance are more stringent than what is currently in place, there is the question of how "good" does the new system have to be compared to the reference system.

The purpose of error rate estimates (VME and ME) is to help clinicians make diagnostic decisions in light of a sensitive or resistant result for the drug/organism combination being evaluated. A little used, but important aspect of the performance of an AST test is its predictive value (PV). For example, if a clinician gets a sensitive test result, the Predictive Value Sensitive is the probability that the organism is truly sensitive to the given drug. Conversely, Predictive Value Resistant is the probability that a resistant result indicates a truly resistant organism. As is true for traditional diagnostic tests, the predictive value of a test is dependent on both the prevalence of resistance occurring for a

particular antimicrobial and the error rates. Table 1 shows the cross-classification of test and reference categorical results in a manner similar to traditional diagnostic tests.

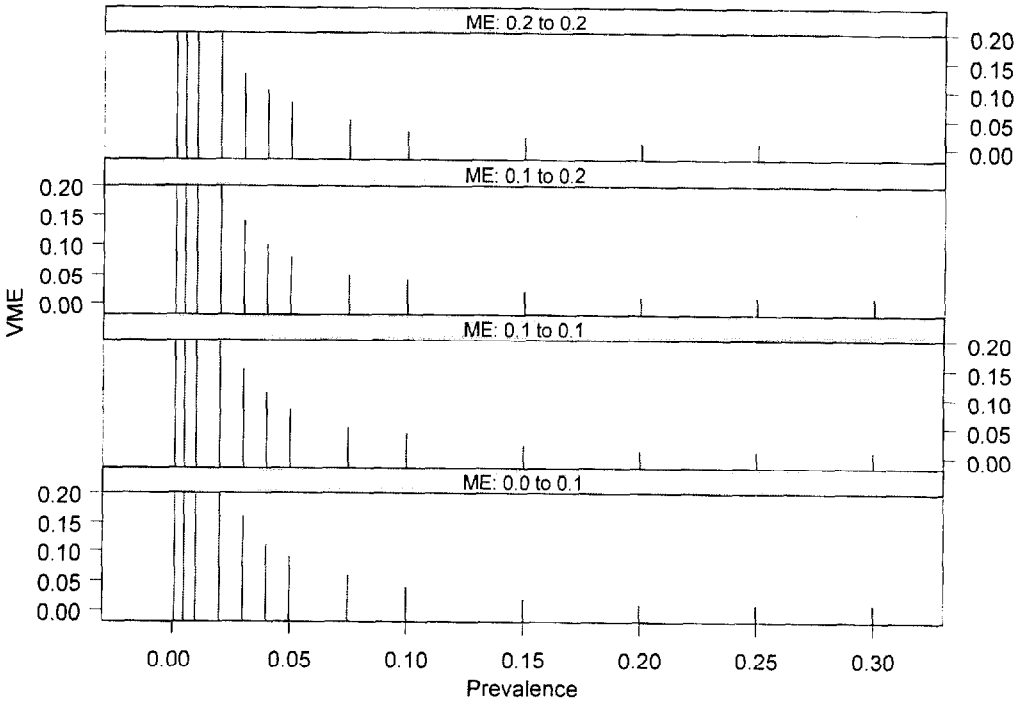
Table 1: Cross Tabulation of Categorical Results for Test and Reference Systems

		Reference System	
		Resistant	Sensitive
New Test	Resistant	% Correct Resistant	%ME
	Sensitive	%VME	% Correct Sensitive
		% Resistant	% Sensitive

To demonstrate the use of predictive value for performance evaluation, suppose 20 resistant strains are tested and the new test correctly classifies 19 of the 20 strains as being resistant to an antimicrobial. The estimated VME rate is 5% with a corresponding 95% confidence interval, 0% – 17%. If, in the same study, the ME rate is estimated to be 3%, the predictive value sensitive is 100% in a population with 0.5% prevalence of resistance to that antimicrobial. From the predictive value perspective, a test sensitive result is highly predictive that the true result is sensitive. Therefore, the chance that a patient would be falsely treated would be extremely low. In fact, the predictive value of a sensitive result is 99.9% even if the VME rate is as high as 17% (upper 95% confidence bound) for a fixed 3% ME rate in the same population.

Predictive values can be used to evaluate proposed acceptable ranges for errors and/or as an additional performance measure for a new AST test. As an example, a search can be done over values of VME, ME and prevalence to find combinations that result in a desired PV Sensitive and/or PV Resistant. Figure 1 shows the results of a search done to find combinations of VME, ME and prevalence that yielded a PV Sensitive result greater than or equal to 99.5%. In this figure, there are four panels showing four ranges of ME rates. VME rates are shown on the y-axis, alternating on the left and right sides by panel for ease of reading. Prevalence is shown on the x-axis. The height of the line at each prevalence point within each ME rate range represents the largest VME that can occur and still yield a 99.5% PV Sensitive. Figure 1 shows that for low prevalence, e.g., prevalence less than 2%, both VME and ME rates can be as high as 20%. On the other hand, for high prevalence situations, both VME and ME rates need to be low.

Figure 1: Results of a search to find combinations of VME, ME and Prevalence rates that result in PV Sensitive ≥ 99.5%. ME and VME rates ranged from 0.01 to 0.2. Prevalence ranged from 0.1% to 30%. Values are in proportions.



Industry Proposal

Industry's position is that the guidance document should address VME rates under the following three scenarios. The study design and performance criteria for error rates may be different under the three situations.

Scenario 1

Prevalence of a specific resistance mechanism is high and the MICs of both test and reference systems are not near the breakpoint. Under this situation, sample size is less of an issue and VME rates can be estimated with the desired precision using the standard study design. An example of this would be demonstrating performance of a system to correctly determine susceptibility of *E. coli* to ampicillin. The resistance in this population is approximately 35%, the required number resistant strains should not be difficult to obtain, and both test and reference systems are highly likely to accurately detect the resistance.

Scenario 2
Prevalence of a specific resistance mechanism is high and the MIC of either the test or reference system is near the breakpoint. Here, sample size is less of an issue; however, the inherent reproducibility of both test and reference systems can be critical. Additional testing in both the test and reference systems may be warranted to establish the distribution of MICs for the particular drug/organism combinations. The study design, including sample size justification for the number of replicates tested and method of data analysis, should be determined in a statistically valid manner.

Scenario 3
The number of resistant strains is small, due, for example, to emerging resistance, so that the developer will not be likely to see many in a general sampling of the population during a clinical trial. The developer, however, would still need to ensure that the test system accurately and reproducibly determines resistance. In this situation, the study should be designed to ensure that false susceptibility is a random occurrence rather than a systematic error with the new test system. One recommendation for doing this would be to use a well-characterized challenge set of strains with the specific resistance mechanism in conjunction with a reproducibility study.

In general, the clinical studies should ensure that the device is reproducible and repeatable across a sample of clinical sites. Clinical studies should also ensure that false susceptibility in the device when tested against strains with known resistance mechanisms is random rather than systematic.

Accordingly, we recommend deleting the reference to Table 5 (Maximum Number of VMEs as Function of the Number of Resistant Strains Tested) and replacing it with language that would allow one to look at error rates in different ways, depending on factors such as prevalence of resistance and proximity to breakpoints.

Alternative Language for Section 12.1.3

A very major error rate greater than 1.5% may be acceptable under some circumstances. Manufacturers will be expected to provide justification to FDA to support the rationale for accepting a VME greater than 1.5%. For example, if a statistically acceptable approach to retesting and incorporating repeat testing results for both the reference and test methods has been devised, the resulting error rates could be considered. A second possibility is to consider the confidence interval for an error rate, in addition to the point estimate. If, for example the VME rate is 2.9% (1/35) and the confidence interval is 0.1% to 14.9%, the length

of the confidence interval or the upper bound of the confidence interval could be considered. It also may be possible to establish the equivalence of the reference and test methods by examining the distributions of MICs at or near the breakpoints for both reference and test methods. If there is adequate statistical power and the distributions are not statistically different, then a contraindication may not be necessary. Another possibility is to apply different error rate limits based on the distance the test result is from the breakpoints.

III. Repeat Testing

FDA's 2000 draft guidance states that repeat testing is an option for determining systematic error, but does not give any guidance on how repeat testing could be done. In addition, there is no guidance as to how the results of repeat testing can be used in looking at discrepancies between reference and test results or whether repeat results can be incorporated into the final performance estimates of EA and CA. The draft guidance also states that repeat testing of challenge and reproducibility strains will not be used.

We believe that repeat testing may be appropriate in certain circumstances and that manufacturers should be allowed to use their discretion in determining which samples should be repeated *a priori*. These circumstances should be defined in the clinical protocol.

Alternative Language for Section 10

Repeat testing of recent clinical isolates and stock strains may be performed to determine if an error is random, procedural (e.g., technique-related), or indicative of a system performance issue (e.g., reproducibility). Repeat testing is appropriate for organism/drug combinations that result in greater than one two-fold dilution discrepancies and major or very major errors.

Repeat testing of reference and test panels should be performed at the test site where the error occurred. The number of repeat tests (duplicate, triplicate, etc.) should be determined by the manufacturer and stated in the study design. Any repeat testing should be done using a different inoculum suspension to inoculate each repeated pair of reference and test panels.

1. Results from each test should be submitted along with the original results. Quality control strains must be included for each day of repeat testing.
2. If only discordant samples are tested, they should be presented separately or justification provided to include repeat results into the final summary.

3. Because retesting of discordant samples alone allows the system under evaluation to determine which samples are being retested, a randomly selected subset of concordant samples for the organism/drug combination may also be retested. The number of concordant samples for retesting should be chosen with a defensible statistical rationale in mind.
4. Although statistically valid analysis methods exist to incorporate initial and retest results in the estimation of error rates, these methods may be complex. Therefore, the manufacturer should describe the method(s) used to combine initial and repeat results into a final summary table and provide the statistical rationale.

IV. Use of Previously Established, "Expected" Results Only to Assess Performance with Challenge Strains

FDA's proposed guidance appears to preclude concurrent testing of challenge strains in both reference and test methods. According to the guidance, "If the organisms have been characterized phenotypically using the NCCLS reference method, this should be used as the "expected result". The requirements for this phenotypic characterization, such as numbers of replicates, runs and media or tray lots, are not described.

FDA further states that "If the 'expected result' is not known the isolates should have multiple MIC testing performed using the reference method only, prior to entering into this study to determine the mode or "expected result". Again, the numbers of replicates, runs, and media lots are not described, but it is clear that a significant effort will be required to determine "true expected" results for a set of challenge strains.

The proposed guidance indicates that the masked challenge set be sent to one site for performance on the test device only. There is no allowance for repeating the test device or for parallel testing by the reference method. Thus, any discrepancy would be assumed to be the fault of the test device when, in fact, the "expected result" or the test conditions may not be perfect (e.g., mixed culture; transcription error; decreased expression of resistance with a stock culture due, for example, to loss of a plasmid).

We propose that the sponsor be given the option of using previously established, "expected results" and/or of performing the reference method concurrently with the test device. This would allow sponsors to use well-characterized, stable isolates in their challenge sets where appropriate. Sponsors could also use strains for which they are highly certain of an on-scale result, but for which sufficient testing has not been done to establish a "true expected" result.

We also recommend that a manufacturer be allowed to include multiple sites in testing challenge strains. Each strain would still only be tested at one site, but the testing would be spread across more than one site.

V. Design of the Precision/Bias Study

The 2000 draft guidance proposes that precision and bias be assessed by testing a minimum of 25 selected organisms one time each at each of three sites, for a total of 75 results. Selected organisms would include organisms for which the drug is intended with known results in the interpretive range and with an additional concentration allowed on each end of the range. Overall agreement with the expected result (i.e., over the three sites) must be 95% or greater (± one dilution).

The 1991 draft guidance also required that overall agreement be 95% or greater. However, the study design involved testing of a strain in triplicate on three separate days at all of the clinical sites. Thus, for a three-site study, there would be 27 replicates of each strain.

We recommend that the number of organisms be increased slightly to 30 and that the acceptance criterion be 90% or greater. A 90% criterion is consistent with the expectations for challenge and fresh clinical/stock isolate testing. Increasing the number of strains from 25 to 30 eliminates questions of rounding (e.g., nine errors with 90 isolates is 90% agreement).

VI. Colony Count Testing Requirements

FDA has proposed that colony counts be done to ensure that the final test concentration of organism will result in the concentration recommended in the reference procedure (broth dilution of approximately 5×10^5 CFU/mL) and test procedure. The draft guidance indicates that ideally this testing would include all quality control (QC) isolates daily, isolates for precision testing, and 10% of the fresh isolates.

We agree that inoculum preparation is an important part of antimicrobial susceptibility testing, but we disagree that colony counts are the only way of insuring proper inoculum preparation. We believe that the FDA Microbiology Devices Advisory Committee was recommending that inoculum preparation be standardized and closely monitored. The panel did not, however, dictate a specific way of monitoring inoculum preparation. One way of doing this is to perform colony counts, another is to use optical devices that have been validated by comparison to colony counts.

As proposed by FDA, the number of colony counts would be a minimum 158 colony counts (see summary table below). If two QC strains were tested, this would increase to 218 colony counts. If any variations to inoculum preparation are used with the test method, an additional 135 colony counts would be needed.

Phase of Testing	Testing Required	Minimum Number Colony Counts
All Quality Control isolates	Minimum 20 at 3 sites, 1 on-scale	60
Isolates for precision testing	25 precision strains at 3 sites	75
10% of fresh isolates	10% of the 75 fresh/recent isolates at 3 sites	23
Variations in inoculation method	Minimum 20 at 3 sites, 1 on-scale 25 precision strains at 3 sites	135

The current NCCLS Document M7-A5 (Section 7.3.1(4)) recommends performing periodic colony counts to ensure conformance with proper procedure and technique in order to achieve the desired final inoculum in the susceptibility test. A target range of 5 x 10^5 CFU/mL for E. coli ATCC 25922 is stated. However, no specifics are provided for the frequency or the types of samples to be tested.

At the June 1999 NCCLS Antimicrobial Susceptibility Subcommittee Meeting, the colony count recommendations were discussed at length. The consensus was that colony counts will vary with different species and that colony counts will vary outside the previously published range (3 to 7 x 10^5 CFU/mL). A specific range has not been established for other organisms. The standard reference method (e.g., quality control ranges, interpretive breakpoints) has been established using inocula adjusted to the turbidity of a 0.5 McFarland Standard. While colony counts with *E. coli* ATCC 25922 are useful to verify proper procedure, technique and turbidity standard quality, they should not be used to adjust or evaluate the appropriateness of the inocula with individual strains for routine susceptibility tests. Moreover, the criteria FDA would use to evaluate colony count data for strains other than *E. coli* ATCC 25922 are not specified in the guidance.

We propose that colony counts be used to verify proper procedure, technique and turbidity standard by performing them with a selected Quality Control strain (e.g., *E. coli* ATCC 25922) at the beginning of a study and periodically during the study (e.g., beginning/middle/end). We believe that this should be sufficient to demonstrate that the inoculation preparation process is in control. Optical devices may be used to assist the user, but should not be required; this is consistent with

the NCCLS standard reference method which recommends, but does not require, their use. Results from the colony counts should be evaluated qualitatively or as a troubleshooting tool because there are no established colony count ranges for organisms other than *E. coli*.

VII. Limitations Required in Labeling and Software

In Section 13.5 of the 2000 draft guidance, FDA provides examples of limitation statements, including the following: "Recommend the use of an alternative method for testing prior to reporting any results (if software driven, results should be blocked from reporting) when the spectrum of activity for any antimicrobial agent includes organisms with unacceptable i) very major error (VME) and/or ii) major error (ME) rate."

In the 1991 draft guidance, there are two types of limitations for performance with clinical isolates, "Use alternate method if critical to patient care (UAM)" for unacceptable categorical errors and "Do not report (DNR)" for low correlation (e.g., < 90% EA or CA). The 2000 draft document combines those two categories into a single, more restrictive limitation. This single use "alternative method/do not report" category is unnecessarily restrictive.

We propose retaining the two categories of limitations where a DNR limitation is more restrictive than a UAM limitation.

A UAM limitation would be included in the labeling for users to determine the appropriate action to take, based on performance of the device in their laboratories, types of organisms isolates in their institutions and potential effects on patient care. For example, a UAM could be used for an ME rate that is higher than the acceptable rate. This will not result in incorrect therapy, but may prevent use of an antimicrobial when it would likely be effective therapy. If the physician chooses to continue to use of this antimicrobial, the user would have the ability to confirm the results with another method.

A DNR limitation would apply to a low correlation (< 90% EA or CA) or a high level of category errors. The labeling would indicate that results should not be reported for these antimicrobial/organism combinations. Suppressions in software may be provided by the manufacturer to help automate this process and ensure compliance, but they may not be available immediately upon release without unnecessarily delaying introduction of the new antimicrobial. It is important to note that there are multiple mechanisms for users to prevent reporting of erroneous results. This may involve reviewing individual reports and user selected suppressions in the AST system software or hospital information system. These are the same mechanisms relied upon by the manual AST system

user to ensure appropriate reporting. Therefore, we believe that flexibility should be allowed in the timing of manufacturer-implemented suppressions in the AST system software.

We recommend that Section 13.5.1 be revised to read as follows and that a new Section 13.5.2 be added.

Alternative Language for 13.5.1 and new 13.5.2

13.5.1 Recommend the use of an alternative method if critical to patient care to confirm results for organisms with unacceptable i) a very major error (VME) rate and/or ii) a major error (ME) rate.

13.5.2 If the percent essential or category agreement is unacceptable, the labeling must state that the applicable antimicrobial/organism combination is contraindicated in the system and results should not be reported.

* * * * * *

We will be happy to clarify any questions you may have regarding these comments and the proposed revisions, and ask that you contact Sharon Cullen (Dade Behring Inc.) at 916-374-3184 or Ross Mulder (bioMerieux, Inc.) at 314-731-8706. We also reiterate our willingness to meet with FDA to discuss our comments and ideas regarding review criteria for AST devices.

Sincerely,

Constance A. Finch, Dr.P.H.
Director, Regulatory Affairs

Attachment (one)

ccs: Sharon Cullen, Dade Behring Inc.
Cynthia Knapp, Trek Diagnostic Systems
Karen Mills, AB Biodisk
Ross Mulder, bioMerieux, Inc.