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DATE: May 30, 2000
TO: Dockets Management Branch (HFA-305)
FROM: Michael A. Pfaller, M.D. *M.A. Pfaller*
RE: Docket No. 00D-0109 Draft Guidance on Review Criteria for Assessment of Antimicrobial Susceptibility Devices

As a Professor of Pathology, and a practicing clinical microbiologist, at the University of Iowa College of Medicine, I read the above draft document on assessment of antimicrobial susceptibility devices with great interest. Our microbiology group here at Iowa spends a considerable amount of time evaluating new antimicrobial agents, developing testing criteria, developing new test methods and evaluating antimicrobial testing instruments. My colleagues, Dr. Ronald N. Jones and Dr. Gary V. Doern and myself all have served in various capacities on the National Committee for Clinical Laboratory Standards (NCCLS) Antimicrobial Testing Subcommittee. Currently, I am a member of the NCCLS Microbiology Area Committee and the Chair of the Antifungal Test Committee. My colleagues and I have a number of concerns and suggestions regarding the draft guidelines (Docket No. 00D-0109). My concerns are listed below and my colleagues will express theirs separately. I hope that you will take these comments into consideration as constructive comments from a concerned and experienced laboratorian.

1. I agree with the proposed guidelines to establish confidence limits for essential agreement. It is notable that the new guidelines are more stringent than those used to approve the current devices now on the market. To apply more stringent criteria to new products and not go back and challenge the existing products to conform to the new guidelines seems unfair. Either the new guidelines should be applied uniformly or the "Essential Agreement" criteria should remain at $\geq 90\%$ and confidence limits established to include 90% as the lower limit of the confidence interval. No current system meets the criteria of $>90\%$ EA and such performance is not particularly relevant clinically. The categorical errors (major and VME) are much more important as is the categorical agreement.
2. Tables 5 and 6 appear to represent new standards, but they are at odds with the text. Table 5 follows the previously established rate of 1.5% for VME and allows up to 7.5% VME (95% CI). Table 6 includes the previously established EA of 90% as the lower limit of the CI. If I read this right, the acceptable EA is $\geq 90\%$ not $> 90\%$ as discussed in #1 above.
3. I agree that the assessment of VME is critical to prevent medical error. TO bring the recommendations in line with NCCLS document M23-T3, I suggest that the limits for VME range from 2% (level of acceptability for MIC vs disk tests results in M23) to 7.5%.

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4. Categorical errors below 90% should be allowed when they are within one dilution of the breakpoint.
5. New assessment criteria: Assessment of data should be limited to the relevant bug-drug combinations and should include all on-scale values, not just those $\pm 2 \log^2$ dilutions of the breakpoints.
6. Repeat testing of discrepant results should be allowed and should include both the reference and the test methods done in triplicate. The new value should be taken into account in resolving discrepancies.
7. A challenge strain collection is essential. The performance of the challenge strain collection should conform to the expected results. If the results are not as expected both reference and test methods should be repeated in triplicate to attempt to resolve the issue.
8. Inoculum density should be standardized during clinical trial testing using optical density devices that have been calibrated against a McFarland 0.5 turbidity standard as specified in NCCLS document M7.
9. The inoculum density check in the reference and test device should be determined using E. coli ATCC 25922. The target density should be 5×10^5 CFU/ml (range $3-7 \times 10^5$ /ml).

Thank you again for the opportunity to comment on the Review Criteria.

/klm



pfell

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