

Butier, Jennie C

From: Spagnuolo, Paula L. [PSPAGNUOLO@PARTNERS.ORG]
Sent: Wednesday, June 07, 2000 12:59 PM
To: 'fdadockets@oc.fda.gov'
Subject: Docket # 00D-0109



Docket 00D-0109.doc

To Whom it May Concern:

Please find the attached Docket # 00D-0109, "Guidance on Review Criteria for Assessment of Antimicrobial Susceptibility Devices", from Mary Jane Ferraro, Ph.D., M.P.H., Director of Microbiology at Massachusetts General Hospital.

I will also Federal Express her comments today and you should receive the package tomorrow.

Thank you.

Paula Spagnuolo

<<Docket 00D-0109.doc>>

Paula Spagnuolo * MGH Microbiology * 617-726-3612 * pspagnuolo@partners.org

00D-0109

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Clinical Microbiology Laboratories
55 Fruit Street, GRB 526
Boston, Massachusetts 02114-2696
Tel: 617.726.3612. Fax: 617.726.5957

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Mary Jane Ferraro, Ph.D., M.P.H.
*Director, Clinical Microbiology Laboratories
Massachusetts General Hospital*

*Associate Professor of Pathology
Associate Professor of Medicine
Harvard Medical School*

June 7, 2000

Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Docket # 00D-0109

Dear Sir or Madam:

I wish to comment on "Guidance on Review Criteria for Assessment of Antimicrobial Susceptibility Devices". Please allow me to state my interest in this area. First, I am the Director of the Clinical Microbiology Laboratory at Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, a position that I have held for 16 years. As the director of a large clinical microbiology laboratory I am convinced that the use of antimicrobial susceptibility devices, especially those with automated features, is a necessity in the era of cost-effective patient care. We have used one of these devices in our laboratory for more than two decades. In addition to my position at MGH, I also currently serve as the Chairholder of the Subcommittee on Antimicrobial Susceptibility Testing of the NCCLS. As you are aware, the role of this NCCLS Subcommittee is to establish standard reference methods (MIC and disk diffusion), which then become the basis on which commercial susceptibility devices are judged. In addition, our Subcommittee is responsible for establishing quality control ranges and for the review of interpretative criteria (breakpoints) for new antimicrobial agents or reassessment of breakpoints for older agents. Because the MIC data from phase 3 clinical trials and phase 4 studies is often obtained using commercial susceptibility devices, the NCCLS has a great interest in the FDA assuring that these devices are reliable and comparable to the standard NCCLS reference methods. Despite my current position at the MGH, and my involvement with the NCCLS, I will be offering personal comments on this guidance document, which may not necessarily represent the position of my institution nor the NCCLS.

I would first like to applaud the FDA in their desire to update the previous Review Criteria for Assessment of Antimicrobial Susceptibility Devices document dated 5/31/91. We have learned a great deal about the pros and cons of these devices in the last decade and I believe that this revision is appropriate at this time.

I offer the following specific comments:

1. Section 1.2, 1st paragraph. Although a separate subcommittee to draft NCCLS document M23 established in 1986, within a few years (ca. 1989), this subcommittee became a working group of the Subcommittee on Antimicrobial Susceptibility Testing. The reference for this paragraph (now # 4) should be reference # (5).
2. Section 1.2, 4th paragraph. The document should provide contemporary references the shortcoming of short incubation tests. If specific individual references cannot be given, then the Manual of Clinical Microbiology, 7th Edition, chapter on Susceptibility Testing Instrumentation and Computerized Expert Systems for Data Analysis and Interpretation could be utilized.
3. Section 4.2 Category Agreement. The FDA may want to consider whether both the FDA interpretive criteria and the NCCLS interpretative criteria (should they differ) be used for establishing category agreement. Although in most instances these interpretative criteria agree, there are certain instances when they differ. For example, the FDA interpretative criteria for cephalosporins and *Streptococcus pneumoniae* are much higher than those of the NCCLS because they were established before penicillin and cephalosporin resistance was recognized to be a major clinical problem. It is conceivable that a MIC system could show category agreement with the much higher FDA MIC interpretative criteria, but not with the current, more stringent, NCCLS interpretative criteria. Other examples of this are also possible.
4. Section 6 Organisms. The FDA may wish to consider whether organisms for which there is no approved drug indication should be allowed to be tested in certain circumstances. Once a drug is approved for clinical use labs are often asked to test related organisms (e.g. enterobacteriaceae) that are not listed in the clinical indication of the label. The organisms tested should at least include those in the in vitro listing.
5. Section 7.7.2, Inoculum Density Check. I believe the quality control checks as indicated in this paragraph are a bit excessive. I agree that a quality control check on *E. coli* ATCC 25922 could be performed on a daily basis, as well as random checks on fresh isolates. Performance of excessive colony counts, on other quality control isolates, or on additional clinical isolates are exceedingly labor-intensive and may result in uninterpretable information. The latest version of the NCCLS documents (M2 and M7 dated January, 2000) indicate the target inoculum density of 0.5 McFarland Standard is for the *E. coli* ATCC 25922.

I believe that inoculum density for short incubation systems should be standardized during clinical trials using some sort of an optical density device. These optical density devices should be calibrated using a 0.5 McFarland Standard as specified in M7. If those steps are followed, then the commercial device should compare quite closely to the NCCLS reference method.

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