DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

05 March 2007

Robert Habig, Ph.D.
President
Clinical and Laboratory Standards Institute (CLSI)
940 West Valley Road
Wayne, Pennsylvania 19087

Dear Dr. Habig:

This letter is in response to your June 21, 2006, petition requesting the following actions: (1) the Center for Devices and Radiological Health (CDRH) "give positive consideration to use of new or revised susceptibility interpretive criteria advocated by Clinical and Laboratory Standards Institute (CLSI) . . . as well as the interpretive criteria in the FDA-approved labels of antimicrobial agents that can be tested by antimicrobial susceptibility test (AST) devices;" and (2) CDRH "positively review" fluconazole disks for disk diffusion susceptibility testing of *Candida* spp. patient isolates for use in clinical laboratories. For the reasons given below, we are granting in part your first request and denying your second request.

The determination of susceptibility test interpretive criteria is an integral part of FDA's regulatory review process of assuring the safety and effectiveness of antimicrobial drug products [21 Code of Federal Regulation (CFR) 314.126]. During the new drug application (NDA) approval process, FDA analyzes nonclinical data (e.g., in vitro activity and animal models of infection), pharmacokinetic/ pharmacodynamic characteristics, and clinical trial results for each antimicrobial drug product intended for human use. Based on its review and analysis of the nonclinical and clinical data, FDA determines *in vitro* susceptibility test interpretive criteria. In addition, FDA also determines the appropriate quality control parameters for susceptibility testing. The results of FDA's analysis are reflected in an approved antimicrobial drug product's labeling, which includes the approved indications and organisms associated with the indications, the recommended antimicrobial dosages, the recommended susceptibility test interpretive criteria, the indicated organisms for susceptibility testing, and quality control parameters for *in vitro* susceptibility testing (see 21 CFR 201.57(c)(2)). Changes in any of these parameters could alter the safety and effectiveness of the use of the antimicrobial drug product and also the performance of the AST device.

While FDA believes that both device and drug labeling should reflect the most current information available, FDA intends to clear all new 510(k)s for AST devices only when such 510(k)s reflect that the AST devices are intended for use with the susceptibility test interpretive criteria in the antimicrobial drug product's label. The agency believes labeling on AST devices should generally be consistent with labeling for the antimicrobial drug products for which the AST devices will be used to test microbial susceptibility.

FDA has revised the Class II special controls guidance document, Antimicrobial Susceptibility Test (AST) Systems, Guidance for Industry and FDA (AST Guidance) (see http://www.fda.gov/cdrh/oivd/guidance/631.pdf) to reflect its intent to clear all new AST devices with susceptibility test interpretive criteria that are consistent with antimicrobial drug product labeling.

However, FDA recognizes that CLSI's frequent examination of peer-reviewed literature and other available clinical and microbiological data evaluating susceptibility information for specific antimicrobial drugs and microorganisms should be considered. This information may lead NDA holders to request changes to the susceptibility test interpretive criteria for their antimicrobial drug product or may lead FDA to request such changes.

As described in the revised AST Guidance, any group or individual, including CLSI, that has adequate information to support susceptibility test interpretive criteria that are different from the susceptibility test interpretive criteria in the antimicrobial drug product labeling may choose to submit to FDA a citizen petition requesting that the label for the antimicrobial drug product be changed to reflect the different susceptibility test interpretive criteria. The petition should state the justification for the different susceptibility test interpretive criteria and include the data on which the different susceptibility test interpretive criteria were based. FDA is committed to reviewing this information in a timely manner, resources permitting. If the antimicrobial drug product label is changed to include the susceptibility test criteria proposed in the citizen petition, FDA intends to support clearance of 510(k)s for AST devices labeled with the changed susceptibility test criteria.

FDA also recognizes that in some cases in the past changes have been advocated by CLSI in susceptibility test interpretative criteria that are different from the antimicrobial drug product's labeling. The agency is considering developing a guidance document that would discuss the agency's intent to exercise enforcement discretion in some circumstances over those AST devices that are labeled for use with susceptibility test interpretive criteria advocated by CLSI or others.

Regarding the request for FDA to "positively review" fluconazole disks, FDA may not discuss or acknowledge the existence of a pending application for device approval, 21 CFR 814.9, or, in general, for device clearance, 21 CFR 807.95(b). As a result, FDA is denying your request. However, we can assure you that CDRH is committed to expeditiously reviewing this type of application when it is submitted to the FDA by AST disk device manufacturers prior to commercial distribution.

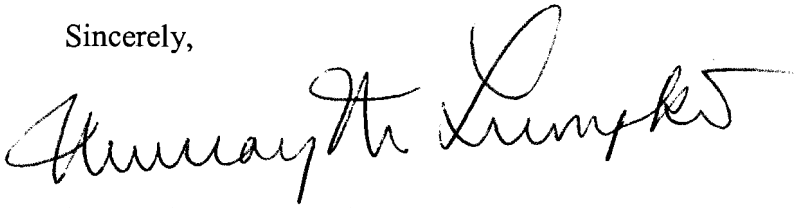
Conclusion

FDA is granting in part your request (1) to "give positive consideration" to CLSI susceptibility test interpretive criteria, along with the susceptibility test interpretive criteria on the antimicrobial drug product label, for AST devices when there are

differences between the CLSI susceptibility test interpretive criteria and the antimicrobial drug product label's susceptibility test interpretive criteria. FDA intends to consider information on alternative susceptibility test interpretive criteria submitted by CLSI through existing processes to request changes to the susceptibility test interpretive criteria in the drug product label. FDA is denying your request (2) to "positively review" fluconazole disks because the agency generally may not discuss or acknowledge any pending application for such a product.

The agency recognizes the important contributions made by CLSI in the area of antimicrobial susceptibility testing, and is committed to continue working with CLSI to provide the healthcare community with safe and effective AST devices. The agency particularly appreciates CLSI's continued efforts in monitoring emerging resistance to antimicrobial drugs. FDA looks forward to a continuing collaboration with CLSI on these issues.

Sincerely,



Murray M. Lumpkin, M.D.
Deputy Commissioner
International and Special Programs