The undersigned organization submits this petition to request two things. First, that applications for clearance to market medical devices used to determine the \textit{in vitro} antimicrobial susceptibility of bacterial and fungal pathogens give positive consideration to use of new or revised susceptibility interpretive criteria advocated by Clinical and Laboratory Standards Institute (CLSI) (formerly the National Committee for Clinical Laboratory Standards [NCCLS]), as well as the interpretive criteria in the FDA-approved labels of antimicrobial agents that can be tested by the device. CLSI has established a preeminent role during the past 34 years in consensus standardization of test procedures, quality control, and interpretive criteria for antimicrobial susceptibility testing. CLSI is recognized for the application of its inclusive, open, and transparent voluntary consensus process to develop global standards for laboratory and other healthcare practices. In addition, CLSI is recognized globally for its responsiveness to emerging trends in patterns of resistance to antimicrobial agents in a variety of bacterial and fungal pathogens. Secondly, this petition requests that the application for clearance of fluconazole disks for disk diffusion susceptibility testing of \textit{Candida} spp. be positively reviewed in order to allow rapid, inexpensive testing of \textit{Candida} spp. patient isolates by clinical laboratories.

A. \textbf{ACTION REQUESTED}

This petition requests two actions. First, that the Commissioner amend the recent practice of assessing the performance of medical devices for determining the \textit{in vitro} susceptibility of bacteria or fungi to various antimicrobial agents using only the criteria included in the approved drug label rather than new or revised criteria published by CLSI. CLSI has an established record of deriving antimicrobial agent interpretive criteria using a panel of experts in clinical microbiology, pharmacology, and clinical infectious diseases from within and outside the U.S. CLSI (formerly NCCLS) has published antimicrobial agent interpretive criteria since 1972 \cite{1} for use by U.S. and non-U.S. clinical microbiology laboratories to interpret the results of susceptibility tests performed according to the standards developed by the organization. With few exceptions, the interpretive criteria included in the CLSI standards and their supplements are identical to those included in the FDA-approved drug labels. However, in a few instances, the CLSI interpretive criteria differ from those of the approved drug label, often due to the emergence of resistance to the drug that has been recognized since the drug label was initially approved that has resulted in a change in the CLSI breakpoints. CLSI has as part of its mission the development of test methods and interpretive criteria that assist in the
recognition of emerging antimicrobial resistance. The FDA Guidance Document (Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test [AST] Systems; Guidance for Industry and FDA, February 5, 2003) for submission of requests for premarket (510[k]) clearance states that “Agreement of interpretive results (SIR) between a new device under evaluation and an NCCLS standard reference method. FDA interpretive criteria should be used but the NCCLS criteria, if different, may also be applied if based on more current recommendations for detecting organism resistance when resistant mechanisms were not recognized (or did not exist) during the FDA drug evaluation.” This guidance document supplements the general controls of the Federal Food, Drug & Cosmetic Act premarket notification requirements described in 21 CFR 807 Subpart E. This petition requests that the CDRH begin again to review submissions that include an assessment of device performance for 510(k) clearance using the current CLSI interpretive criteria, as well as the FDA drug label criteria in those few instances where differences exist.

Secondly, CLSI has assumed a global leadership role in developing testing methods and interpretive breakpoints for both minimal inhibitory concentration (MIC) and disk diffusion testing of antifungal agents. Guidance for laboratory testing of antifungal agents and interpretive criteria are currently not provided in FDA-approved labels of antifungal agents. The FDA Center for Devices and Radiological Health (CDRH) has cleared two devices for determining the minimal inhibitory concentrations (MICs) of four antifungal agents (including fluconazole), but has not favorably acted on the application to clear fluconazole susceptibility testing disks. The fluconazole disk test described by CLSI is a much simpler and less expensive approach to testing that agent, and could be performed by virtually any competent clinical microbiology laboratory. Clearance of fluconazole disks would make routine antifungal susceptibility testing of *Candida* spp. clinical isolates readily available to facilitate patient care.

Specifi ally, this petition asks that:

• CDRH clear susceptibility test devices, especially those with software providing interpretive criteria that would permit clinical microbiology laboratory directors and their medical staff to choose to apply either the FDA or the latest CLSI interpretive criteria for reporting of their susceptibility results.

• CDRH clear fluconazole disks for performance of rapid, cost-effective antifungal susceptibility testing of yeasts by clinical laboratories.

B. STATEMENT OF GROUNDS

The following analysis includes a summary of the methods used by CLSI in establishing or revising interpretive criteria for tests that result in MIC determinations or disk diffusion test categories. The current clinical laboratory regulatory requirements that allow use of either FDA or CLSI interpretations are also summarized.
The Clinical and Laboratory Standards Institute (formerly NCCLS) has worked continuously since the formation of the first susceptibility testing subcommittee in 1968 to provide performance standards for antimicrobial susceptibility testing for use by clinical microbiology laboratories. Over the years, the Antimicrobial Susceptibility Testing Subcommittee has worked to refine the process of establishing interpretive criteria or “breakpoints” for both quantitative broth and agar dilution tests that give rise to minimal inhibitory concentration (MIC) values that must be interpreted for clinical application, as well as the disk diffusion test that results in drug inhibition zone diameters that must be deciphered using a standard set of interpretations (2, 3, 4). The Antifungal Susceptibility Testing Subcommittee was formed later, but develops MIC and disk diffusion interpretive criteria in exactly the same manner. These interpretive criteria are used by almost every clinical microbiology laboratory in the U.S., and by many laboratories in Canada, Latin America, Europe, Australia, Asia, and Africa. The American National Standards Institute (ANSI) accredits the CLSI susceptibility testing standards as U.S. National Standards. During this 34-year period, CLSI has earned the reputation of the world’s leading organization in setting antimicrobial susceptibility testing breakpoints.

The CLSI subcommittees review an extensive amount of microbiology, pharmacology, and clinical therapy data in establishing or revising breakpoints. The data review is outlined in detail in CLSI/NCCLS document M23-A2—Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters; Approved Guideline—Second Edition, 2001 (5). The document describes the types of data used for defining breakpoints, including:

- **Microbiology data**, including MICs and zone diameters for wild-type organisms within the spectrum of activity and intended use of the antimicrobial agent; MICs and zone diameters of strains that contain well-recognized resistance mechanisms that affect the drug class.

- **Pharmacokinetic and pharmacodynamic data**, including levels of the drug in various body fluids and tissues of normal volunteers and in patients. Also included are determinations of serum protein binding and serum half-life determinations. These values are integrated with knowledge of how the drug class is known to kill microorganisms, i.e., concentration-dependent or time-dependent killing in order to arrive at values that compare the peak drug levels to MICs, the area under the drug concentration curve (AUC), and the time above MIC in the body fluid. Mathematical simulations that can be performed to determine the likelihood of achieving the target pharmacodynamic parameter in a patient population at various MIC values are also employed as part of the overall analysis.

- **Clinical response data**, including clinical and microbiological response data that relate drug MICs or zone diameters with successes or failures of treatment as determined during the clinical trials leading up to submission of the New Drug Application to the FDA. However, unlike the position of the FDA, CLSI
continuously reviews clinical data published in the peer-reviewed literature that describes clinical response data for a drug with specific organisms that may reflect emerging resistance to the drug under assessment. In this way, CLSI is uniquely positioned to revise interpretive breakpoints when significant new mechanisms of resistance emerge after the initial FDA approval of a drug and its widespread clinical use. Examples of emerging resistance that have prompted action by CLSI to revise earlier breakpoints include extended-spectrum cephalosporin resistance in *Streptococcus pneumoniae*, fluoroquinolone resistance in *Streptococcus pneumoniae*, vancomycin resistance in *Enterococcus* spp. and more recently in *Staphylococcus aureus*, and fluoroquinolone resistance in staphylococci. CLSI has also established initial MIC and disk diffusion breakpoints for several antifungal drugs for which there are no FDA package insert testing criteria.

The FDA Center for Drug Evaluation and Research (CDER) has statutory responsibility for approving the susceptibility testing interpretive criteria that appear in initial approved drug labels. However, it is not clear that CDER has a mechanism of its own to modify interpretive criteria in response to emerging resistance that may be recognized after drugs are put into clinical use. CLSI has experience in establishing or revising breakpoints gained during more than three decades of developing antimicrobial susceptibility testing standards for clinical laboratories. The FDA-approved drug package inserts reference the CLSI/NCCLS testing methods and quality control measures as being the relevant national standards. While the FDA has the statutory obligation to regulate the content of drug labels, including the susceptibility breakpoints included therein, the CLSI and FDA breakpoints are identical for the vast majority of antibacterial agents in current use. Where differences exist, it usually reflects CLSI’s ability to respond promptly to emerging resistance by appropriately adjusting interpretive breakpoints, or by devising special testing protocols for recognizing resistance (e.g., tests for extended-spectrum beta-lactamases in members of the *Enterobacteriaceae*, vancomycin and oxacillin screening agars, screening tests for high-level aminoglycoside resistance in enterococci) (4). Beyond this, CLSI is unique in providing interpretive criteria for antifungal agents. Susceptibility testing guidance and interpretive criteria have not been included in FDA-approved labels of antifungal agents.

Clinical laboratories look to CLSI as the one authoritative source for all information necessary to perform reproducible and clinically relevant susceptibility determinations on bacteria and fungi. CLSI describes precisely how reproducible testing should be performed, provides quality control ranges to ensure accurate results, offers advice on troubleshooting of technical problems that can arise, and provides guidance on reporting results to clinicians. Laboratories know that they can count on yearly updates (4) of the tabular materials from the two main susceptibility testing documents (2, 3) that will include agents in clinical use and new information needed to recognize emerging resistance. Laboratories generally do not find it convenient to review individual
drug package inserts to locate specific quality control or breakpoint information. Useful information is lacking or out of date with some older agents for which CLSI provides up-to-date information. As stated, antifungal drug labels do not include susceptibility testing criteria, although CLSI has widely accepted documents that describe MIC and disk diffusion testing of some yeast fungi, and MIC testing of filamentous fungi (6, 7, 8, 9, 10).

National regulatory agencies or accrediting bodies, such as the Centers for Medicare and Medicaid Services and the College of American Pathologists that inspect and regulate practices in U.S. clinical laboratories, require that laboratories utilize methods that are consistent with the latest CLSI standards, including quality assurance practices. Those accrediting agencies allow clinical laboratories to interpret susceptibility test results using either FDA package insert values or the breakpoints recommended by CLSI.

The majority of U.S. clinical laboratories employ an FDA-cleared medical device for their routine susceptibility determinations, most often a broth microdilution panel or card that is read either manually or more often using a proprietary instrument. All such devices must be cleared by the FDA Center for Devices and Radiological Health (CDRH) using the paragraph 510(k) notification. The FDA has created the guidance document for use by the diagnostics industry, The FDA Guidance Document (Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test [AST] Systems; Guidance for Industry and FDA, February 5, 2003). This document supplements the general controls of the Federal Food, Drug & Cosmetic Act premarket notification requirements described in 21 CFR 807 Subpart E. The document states that “Agreement of interpretive results (SIR) between a new device under evaluation and an NCCLS standard reference method. FDA interpretive criteria should be used but the NCCLS criteria, if different, may also be applied if based on more current recommendations for detecting organism resistance when resistant mechanisms were not recognized (or did not exist) during the FDA drug evaluation.” The CDRH followed that directive for evaluation of new devices or updates to existing devices until approximately 18 months ago, when susceptibility testing device manufacturers were told that their devices must use the same breakpoints found in the drug’s package insert. In some cases, more up-to-date recommendations exist in the latest CLSI standards that reflect adjustments made in response to emerging resistance. This has the potential to put patients at risk, if the test device does not take into account means to detect emerging resistance to the drug that has been outlined in the CLSI national standards and reflected in updated interpretive breakpoints. This petition specifically requests that the CDRH begin again to positively consider submissions that include an assessment of device performance for 510(k) clearance using current CLSI interpretive criteria, as well as the FDA drug label criteria in those few instances where differences currently exist.

CLSI provides MIC interpretive criteria for four antifungal agents for *Candida* spp. at present, i.e., fluconazole, flucytosine, itraconazole, and
voriconazole (7). In addition, CLSI has published disk diffusion breakpoints for testing *Candida* spp. with fluconazole and voriconazole (9). The rationale for development of the fluconazole MIC and disk diffusion breakpoints has recently been outlined in a peer-reviewed publication (11). The CDRH has cleared two commercial devices for determining fluconazole, fluconazole, and itraconazole MICs with *Candida* spp. However, the CDRH has not cleared commercially prepared disks for diffusion testing of fluconazole, despite the fact that disk testing is a far less costly and much more practical method for use in clinical laboratories. Disks for antimicrobial susceptibility testing are classified in section 21 CFR 866.1620. The availability of disks for testing fluconazole has the potential to significantly reduce an institution’s costs for antifungal therapy, by allowing use of an inexpensive agent (fluconazole) as opposed to much more expensive agents such as the echinocandins or lipid amphotericin B preparations, if susceptibility to fluconazole can be demonstrated by testing individual *Candida* spp. isolates. **This petition asks that industry applications for premarket approval of fluconazole disks be favorably reviewed in light of the existence of the approved-level CLSI documents describing appropriate testing and in light of the prior clearance of the more expensive MIC devices for testing antifungal agents by the CDRH.**

**References**


C. ENVIRONMENTAL IMPACT

The requested relief does not require an environmental assessment or environmental impact statement under 21 CFR § 25.31.
D. ECONOMIC IMPACT

As provided in 21 CFR 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

The undersigned certifies that, to the best of their knowledge and belief, this petition includes all information known to the petitioner that is unfavorable to the petition.

Sincerely,

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Attachments