

June 7, 2007

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

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CITIZEN PETITION

The undersigned organization submits this petition in response to statements included in Section XII G of the revised FDA CDRH guidance document of March 7, 2007 that states "The AST device should be labeled with a breakpoint that is consistent with the breakpoint on the antimicrobial drug label. FDA encourages any group or individual that supports a breakpoint that is different from the one on the antimicrobial drug labeling, to submit to FDA a citizen petition requesting that the label for the antimicrobial drug be changed to reflect the different breakpoint." Rather than attempting to update the labels of a number of older antimicrobial agents where scant clinical data would be available for review in support of changes in the drug labels, we request that the CDRH reconsider its position regarding the requirement that applications for clearance to market medical devices used to determine the *in vitro* antimicrobial susceptibility of bacterial pathogens must incorporate only the approved drug label interpretive breakpoints for reporting test results to clinicians. As outlined in the attached table, there are a number of situations in which the current approved drug labels for commonly prescribed antimicrobial agents include outdated or unhelpful guidance on antimicrobial susceptibility testing and reporting. These fall into three categories, 1) out of date information for testing potentially life-saving drugs for serious infections that fail to take into account emerging resistance in important pathogens (e.g., penicillin, cefazolin, ceftazidime, vancomycin), 2) Lack of critical information for determining and interpreting MIC susceptibility test values (e.g., provision of only disk diffusion testing criteria for ampicillin, oxacillin, gentamicin, amikacin), or 3) lack of specific interpretive breakpoints for important pathogens included in the drug label, possibly leading to inaccurate classification of the susceptibility of important pathogens such as *Streptococcus pneumoniae* or *S. pyogenes* (e.g., imipenem, meropenem, erythromycin). This petition asks that in those instances where the current drug label provides insufficient or out of date test interpretive criteria, that the use of the susceptibility interpretive criteria advocated by Clinical and Laboratory Standards Institute (CLSI) (formerly the National Committee for Clinical Laboratory Standards [NCCLS]) be allowed in order to provide safe and clinically-relevant reporting of susceptibility test results to clinicians. As illustrated in the attached Table, presently cleared susceptibility testing devices utilize the CLSI MIC breakpoint criteria in those instances where the drug label is incomplete or outdated. It would represent a serious degradation of medical practice and increase the risk of administering inappropriate antimicrobials to patients if manufacturers of new devices or manufacturers wishing to update their existing devices were required to follow obsolete drug labels.

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A. ACTION REQUESTED

This petition requests that the CDRH clear new susceptibility test devices or modification of existing devices using CLSI interpretive breakpoints in those instances when the approved drug label of an agent contains incomplete or out of date information regarding susceptibility testing. This would require the Commissioner to amend the recently updated guidance document, *The FDA Guidance Document (Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test [AST] Systems; Guidance for Industry and FDA, March 7, 2007)* for assessing the performance of medical devices for determining the *in vitro* susceptibility of bacteria 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 has published antimicrobial agent interpretive criteria since 1972 (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 relatively 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 (see attached Table), 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, or because MIC interpretive criteria are missing entirely from the approved drug label. CLSI has as part of its mission the development of test methods and interpretive criteria that assist in the recognition of emerging antimicrobial resistance.

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 criteria in those instances where differences exist with FDA drug label. This had been the practice of CDRH for approximately two decades until application of the then existing guidance document began to change approximately two years ago. This change in interpretation was then codified in the recent March 7, 2007 revision of the document.

Specifically, this petition asks that:

- **CDRH modify its recent decision and allow new or modified susceptibility test devices, especially those with software providing interpretive criteria, to be cleared using the latest CLSI interpretive breakpoint criteria in those instances where the approved drug label does not include sufficient information to provide safe and clinically-relevant information on drug susceptibility determinations to clinicians.**

B. STATEMENT OF GROUNDS

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 interpretive breakpoints have been used in FDA-cleared devices for the past two decades. If the recent FDA decision to incorporate only approved drug label breakpoints in cleared devices is followed strictly, laboratories will be unable to report meaningful susceptibility data for a significant number of drugs in current use.

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). 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 majority of American clinical microbiology laboratories utilize the CLSI MIC interpretive breakpoints because they are embedded in the software of FDA-cleared automated or mechanized test devices. It has been the practice to incorporate the CLSI breakpoints in cleared devices for approximately two decades, with the practice only reverting to strict adherence to the drug label breakpoints occurring over the past two years.

The CLSI AST subcommittee reviews 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 for wild-type organisms and those with well-recognized resistance mechanisms that affect the drug class within the spectrum of activity and intended use of the antimicrobial agent described in the approved drug label.
- Pharmacokinetic and pharmacodynamic data, including levels of the drug in various body fluids and tissues of normal volunteers and in patients collected during the New Drug Application studies leading to licensure of the drug. 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.

- Clinical response data, including clinical and microbiological response data that relate drug MICs with successes or failures of treatment as determined during the clinical trials leading up to submission of the New Drug Application to 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 *Staphylococcus aureus*, and fluoroquinolone resistance in *Staphylococcus aureus*.

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 labels 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 majority of antibacterial agents in current use. The CLSI has recently established the policy that it will review and usually publish the initial FDA approved breakpoints of new antimicrobial agents. However, the CLSI is uniquely positioned to reassess interpretive breakpoints two or more years after a new drug has been put into widespread clinical use, and if necessary to adjust interpretive breakpoints.

Clinical laboratories look to CLSI as the one authoritative source for all information necessary to perform reproducible and clinically relevant susceptibility determinations. 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 labels 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 shown in the attached Table.

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 drug label 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 recently updated 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*, March 7, 2007). This document supplements the general controls of the Federal Food, Drug & Cosmetic Act premarket notification requirements described in 21 CFR 807 Subpart E. The revised document states that “The AST device should be labeled with a breakpoint that is consistent with the breakpoint on the antimicrobial drug label.” However, a review of the drug label breakpoints of at least 10 of the 30 most commonly prescribed antimicrobial agents in the accompanying Table demonstrates that some labels lack MIC interpretive criteria or contain outdated information. In those instances, more up-to-date recommendations exist in the latest CLSI standards. This has the potential to put patients at risk, if the test device does not take into account means to detect emerging resistance, or if breakpoints for important pathogens are lacking. **This petition specifically requests that the CDRH begin again to allow an assessment of device performance for 510(k) clearance using current CLSI interpretive criteria in those instances where there is insufficient information in the drug label.**

References

1. NCCLS. *Performance Standards for Antimicrobial Disk Susceptibility Tests; Proposed Standard*. M2-T. National Committee for Clinical Laboratory Standards, Villanova, PA, 1972.
2. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Seventh Edition*. CLSI document M7-A7 [ISBN 1-56238-587-9]. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2006.

3. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard—Ninth Edition*. CLSI document M2-A9 [ISBN 1-56238-586-0]. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2006.

4. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing; Sixteenth Informational Supplement*. CLSI document M100-S16 [ISBN 1-56238-588-7]. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2006.

5. Clinical and Laboratory Standards Institute/NCCLS. *Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters; Approved Guideline—Second Edition*. CLSI/NCCLS document M23-A2 [ISBN 1-56238-435-X]. Clinical and Laboratory Standards Institute/NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2001.

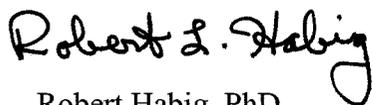
C. ENVIRONMENTAL IMPACT

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.



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Sincerely,



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Attachments