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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." This petition is submitted in parallel to a petition submitted to the Center for Drug Evaluation and Research (CDER) that requests the official drug labels of penicillin G potassium and sodium and the label for oral penicillin V potassium be updated with additional antimicrobial susceptibility breakpoints. Specifically, it has been proposed that CDER create a second set of interpretive breakpoints for the parenteral drug penicillin G when tested against nonmeningitis isolates of *Streptococcus pneumoniae*, and to add breakpoints to the official label of oral penicillin V potassium. It has long been recognized that the current FDA approved drug label and Clinical and Laboratory Standards Institute (CLSI) interpretive breakpoints for penicillin G underestimate the clinical utility of the drug for treatment of common infections other than meningitis, e.g., community acquired pneumonia (CAP). The petition to CDER proposes that the presently approved FDA and CLSI breakpoints be retained and designated as for "meningitis," and that a second set of higher breakpoints be included in the approved penicillin G potassium and penicillin G sodium drug labels that are designated as for "nonmeningitis." For completeness, the penicillin G potassium and sodium labels should include the same meningitis breakpoints, since the current drug label for penicillin G potassium indicates a susceptible MIC breakpoint for all streptococci of ≤ 0.1 $\mu\text{g/ml}$ and a resistance breakpoint of ≥ 4 $\mu\text{g/ml}$. These are one dilution higher than those in the penicillin G sodium label. In addition, it is requested that the drug label of oral penicillin V potassium be updated to include only the lower breakpoints ($S \leq 0.06$, $I = 0.1-1$, $R \geq 2$ $\mu\text{g/ml}$) that are used to determine susceptibility to parenteral penicillin G for meningitis. This petition asks that if the petition to CDER is denied or implementation is delayed, that CDRH allow clearance of diagnostic devices for antimicrobial susceptibility testing to be cleared through the 510(k) process for marketing in the U.S. by incorporation of the newly approved Clinical and Laboratory Standards Institute (CLSI) penicillin breakpoints described above and in the attached Table 2G.

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A. ACTION REQUESTED

This petition requests that CDRH allow 510(k) clearance of devices for antimicrobial susceptibility testing of *Streptococcus pneumoniae* with penicillin to be based upon performance criteria using the newly approved nonmeningitis interpretive breakpoints as well as the existing meningitis breakpoints if there is a decision by CDER not to update the official drug labels of the various formulations of penicillin, or if the revision of the labels will be delayed. The FDA and CLSI meningitis breakpoints for penicillin are susceptible ≤ 0.06 $\mu\text{g/ml}$, intermediate = 0.12-1 $\mu\text{g/ml}$, and resistant ≥ 2 $\mu\text{g/ml}$. The newly approved CLSI nonmeningitis breakpoints are susceptible ≤ 2 $\mu\text{g/ml}$, intermediate = 4 $\mu\text{g/ml}$, and resistant ≥ 8 $\mu\text{g/ml}$. The breakpoints approved by CLSI for penicillin V potassium for oral administration are the same as the meningitis breakpoints above.

B. STATEMENT OF GROUNDS

The Clinical and Laboratory Standards Institute (formerly NCCLS) has a long established reputation in consensus standardization of test procedures, quality control, and interpretive criteria for antimicrobial susceptibility testing. CLSI 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 (1, 2, 3). 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 standards organization in setting antimicrobial susceptibility testing breakpoints. The majority of American clinical microbiology laboratories utilize the CLSI MIC interpretive breakpoints because they are included in the software of current FDA-cleared automated or mechanized test devices

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 (4). 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, CDER does not have a mechanism in place to periodically review and when needed 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. 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. The FDA Deputy Commissioner has recently stated that CDER would like to receive citizen's petitions if individuals or organizations believe that drug labels need to be updated. Therefore, CLSI has filed a citizen's petition that requests that the official labels for intravenous penicillin G potassium and penicillin G sodium should be updated with breakpoints that reflect the susceptibility of pneumococci involved in infections other than meningitis. It was further requested that the official drug label of oral penicillin V potassium be updated by indication that

susceptibility to that form of penicillin should be based on application of the meningitis breakpoints for *S. pneumoniae*. This petition asks CDRH to clear diagnostic devices for determining the susceptibility of *S. pneumoniae* to penicillin using the CLSI meningitis and nonmeningitis breakpoints, if there will be a delay in updating the FDA drug labels of the various penicillin formulations, or if CDER denies the CLSI petition request. The materials reviewed by the CLSI AST Subcommittee leading to the decision to adopt a second set on nonmeningitis breakpoints for intravenous penicillin G potassium and sodium are attached to this petition.

References

1. 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]. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2006.
2. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard—Ninth Edition*. CLSI document M2-A9 [ISBN 1-56238]. 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 Susceptibility Testing; Seventeenth Informational Supplement*. CLSI document M100-S17 [ISBN 1-56238]. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2006.
4. 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]. Clinical and Laboratory Standards Institute/NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2001.

C. ENVIRONMENTAL IMPACT

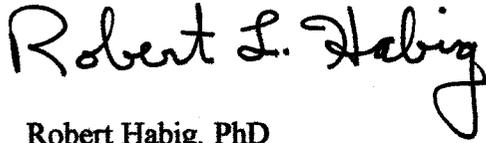
The requested relief does not require an environmental assessment or environmental impact statement under 21 CFR § 25.31.

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.

Sincerely,



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