Dr. John Farley, M.D., M.P.H
Office Director
Office of Infectious Diseases
Office of New Drugs
Center for Drugs Evaluation and Research
United States Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

Dear Dr. Farley:

We, the undersigned organizations are writing to bring your attention to the current process for updating antimicrobial susceptibility interpretive criteria (commonly referred to as 'breakpoints') which are used to define pathogens as susceptible or resistant to an antibiotic. As you know, more than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result.[1] We are increasingly concerned that updated breakpoints are not being recognized by the agency in a timely manner, putting patients at risk and compromising diagnosis and treatment of infections. It is critical that we work together to determine how to speed up the process for updating breakpoints. **To that end, we would like to request a meeting with you and your team to discuss these concerns in greater depth and how we can assist in forging a path forward.**

As you know, it is important that breakpoints updates are recognized by FDA as they are updated, in order for manufacturers to obtain clearance of test devices with these updated standards. In the absence of an FDA-recognized breakpoint, laboratories are forced to either apply off-label testing or use grandfathered tests, which in many cases are obsolete.

Recognizing the challenges to accomplishing these updates in a timely manner without additional clinical drug trial data, Congress passed the 21st Century Cures Act (Cures) in 2016 and included language aimed at improving the process. The Cures provisions allowed the FDA to accept update requests and scientific rationale from entities other than drug sponsors along with an effort to codify the recognition of breakpoints from the recognized standards development organization (SDO), the Clinical Laboratory Standards Institute (CLSI). However, we have concerns that this change has not resulted in a significant increase in the Center for Drug Evaluation and Research's (CDER) acceptance of current, updated breakpoints which puts patients at high risk and increases the likelihood of disease transmission and proliferation of antibiotic resistant infections.

One example of a current challenge in patient care is the testing and reporting of daptomycin for *Enterococcus faecium* . Daptomycin is currently approved by the FDA at a dose of up to 6 mg/kg/d for *Staphylococcus aureus* and 4 mg/kg/d for *E. faecalis*. It was never approved for the treatment of infections caused by *E. faecium*, largely because there were insufficient cases in the registration trials to set a breakpoint. Yet, as time has evolved, a primary clinical use of daptomycin is for the treatment of *E. faecium* infections, and recent PK/PD data have shown that doses of **8-10 mg/kg/d** are needed for clinical success. However, this regimen is only effective for isolates with MICs below 8 mcg/mL, requiring susceptibility testing. In cases such as these, effective treatments for resistant organisms can be found

[1] CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019 DOI: http://dx.doi.org/10.15620/cdc:82532. Available from: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

through an off-label use of a drug, but are hampered by the lack of testing options, leading clinicians to prescribe 'in the dark'.

A lack of official acknowledgment of these life-saving breakpoints impedes clinicians from implementing best practices for their patients and to protect public health. We need a clear path forward not only for breakpoint updates, but also for "bug/drug" combinations that are routinely tested and reported using CLSI breakpoints and for which there are no FDA breakpoints. Collaboration with CDER, CDRH and external stakeholders is essential to accomplishing these goals, and our organizations are eager to be part of the solution.

We recognize that this is a complex issue which requires careful consideration. As organizations with a vested interest in ensuring updated breakpoints and protecting the health of patients, we would appreciate the opportunity to discuss our concerns in greater depth with you in the hopes we might develop solutions to the problem. Please contact Anna Scrimenti, ASM Senior Regulatory Affairs Specialist at ascrimenti@asmusa.org.

Sincerely,

American Society for Microbiology
College of American Pathologists
Infectious Diseases Society of America
Society of Healthcare Epidemiologists of America

CC: Jeff Shuren, Tim Stenzel