

Appendix A

A Minimal Validation Study for Application of Revised CLSI Beta-Lactam Breakpoints to Interpret Lower Range MICs Generated by a Commercial Susceptibility Device

The purpose of a validation (verification) study is to determine that accurate results are generated using a commercial diagnostic device in accordance with the manufacturer's performance claims for that device. The Clinical and Laboratory Standards Institute (CLSI) published revised (lowered) MIC breakpoints for five extended-spectrum cephalosporins and aztreonam for members of the Enterobacteriaceae in January 2010. The CLSI also published revised breakpoints for three carbapenems and new breakpoints for doripenem in June 2010. There will be a prolonged period between the publication of these revised interpretive criteria and FDA-clearance of commercial antimicrobial susceptibility testing devices that automatically apply the revised breakpoints for MIC interpretations.

In the interim period, a laboratory could choose to manually interpret MICs on isolates of Enterobacteriaceae using the revised CLSI breakpoints. Alternatively, a laboratory could modify their instrument's software, or use Laboratory Information Software or Hospital Information Software calculations, to provide automatic interpretations of such tests if the device includes drug concentrations that encompass the new CLSI breakpoint concentrations. The purpose of a brief validation study would be to ensure that susceptibility testing results generated by the device and interpreted using the revised CLSI breakpoints are comparable to a reference CLSI method. A laboratory could perform a verification study using as few as 30 selected Enterobacteriaceae isolates by testing them in parallel using the commercial device and a reference CLSI broth or agar dilution or disk diffusion test method.

Test isolates: Ideally, the 30 test isolates should include 5 extended-spectrum beta-lactamase and/or carbapenemase-producing isolates (e.g., *K. pneumoniae* ATCC 700603 that produces SHV-18 and *K. pneumoniae* ATCC BAA 1705 that produces KPC-2), 5 isolates with elevated cephalosporin or carbapenem MICs that do not produce a specific carbapenemase (e.g., *K. pneumoniae* ATCC BAA 1706), and 20 cephalosporin and carbapenem susceptible isolates.

Analysis of data: The category results (i.e., susceptible, intermediate, or resistant) determined by applying the revised CLSI breakpoints to the device-generated MICs and the category results provided by the CLSI reference method (either MIC or disk tests) should agree for $\geq 90\%$ of results. Very Major errors (false susceptibility) should not occur when applying the new breakpoints to the device-generated MICs.