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Methods for antibacterial susceptibility testing

Debio 1452 MIC quality control range with *Staphylococcus aureus* ATCC 29213 using a multi-laboratory study design

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Objectives: To conduct a study to establish MIC quality control (QC) ranges for Debio 1452 (formerly AFN-1252), the active form of the prodrug Debio 1450 (formerly AFN-1720) using the reference CLSI broth microdilution (BMD) method. This FabI inhibitor is being developed for the treatment of staphylococcal infections including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Debio 1452 specifically targets the FabI enzyme in *Staphylococcus* spp. and demonstrates limited activity against other bacterial species.

Methods: An eight laboratory study design was compliant with CLSI M23-A3 guidelines. One QC strain was tested (*S. aureus* ATCC 29213 [SA]) using four media lots (three manufacturers) of cation-adjusted Mueller-Hinton broth (MHB). Frozen-form broth microdilution panels were manufactured at TREK Diagnostics (Cleveland, Ohio, USA). Ten replicate tests were performed generating 320 BMD MIC values. Rifampin was used as a control agent and all results were within the published QC limits (320 values). Colony counts were performed by each participating laboratory.

Results: A four $\log_2$ dilution QC range of 0.002 – 0.015 mg/L was required for *S. aureus* with Debio 1452 due to a dominant "shoulder" MIC at 0.004 mg/L, which had 70.6% of the MIC values compared to the modal occurrences at 0.008 mg/L. Only one value was outside of the proposed range at 0.03 mg/L with 99.7% of all values included in the proposed range. Average colony count of all laboratories was 3.4×10^5 CFU/ml. No significant MIC differences were noted among MHB lots for Debio 1452. All media lot modes were either 0.004 (1) or 0.008 (3) mg/L. The results were analyzed using the Range Finder statistical program to identify outlier laboratories, but none were identified. Quality control results for the control agent, rifampin, ranged from 0.004-0.015 mg/L in complete agreement with the published CLSI QC range. The mode was 0.004 mg/L (67.8% of results) and 31.9% of values were at 0.008 mg/L. All media lots exhibited the identical mode for rifampin of 0.004 mg/L. The CLSI Subcommittee on Antimicrobial Susceptibility Testing approved this Debio 1452 QC range for *S. aureus* ATCC 29213 in January 2011 for publication after the selection of the compound's official chemical name.

Conclusions: Proposed MIC QC range for Debio 1452 should accurately guide microbiologic testing in research laboratories and in clinical or reference laboratories participating in the testing of clinical trial staphylococcal isolates when applying the CLSI BMD method.