WCK 4282 (High-Dose Cefepime-Tazobactam) Disk Diffusion Quality Control Ranges Using a Multi-Laboratory Study Design

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Background: A multi-laboratory study was established to study disk diffusion (DD) quality (QC) ranges for WCK 4282 (tazobactam-cefepime) using a 30/20 µg (2 manufacturers) and the reference DD method. WCK 4282 is under clinical development for the treatment of serious Gram-negative infections.

Methods: An eight-laboratory study design followed CLSI M2-A4 guidelines. Five QC strains were tested (Escherichia coli ATCC 25922, E. coli NCTC 13353, Staphylococcus aureus ATCC 29213, Pseudomonas aeruginosa ATCC 27853). Ten replicates of each QC strain were tested using three different lot numbers of MH agar from three different manufacturers (three manufacturers). Ten replicate disk/diffusion media sets were tested. Each laboratory used the same sucrose-negative (SN) organism generating 400 zone diameters (400 total results). Cefepime and piperacillin-tazobactam control disks were used as control agents.

Results: The zone diameter QC range for cefepime-tazobactam disk data from eight laboratories when testing against E. coli ATCC 25922 was 21.4 to 37.3 mm. The zone diameter QC range for the piperacillin-tazobactam cefepime disk test from eight laboratories was 28.0 to 39.7 mm (21.0 to 47.5 mm). These data were used as the basis for the proposed QC ranges, providing validated internal controls for the QC reference strains, as follows: JMI Laboratories, North Liberty, Iowa, USA (R.N. Jones, M.D., G. Denys, Ph.D., C. Hinton, M.D., and B. Huband), Merck & Co., Inc., Sharpstown, Philadelphia, Pennsylvania, USA (E. Munson, Ph.D.).

Conclusions: These QC ranges should accurately reflect the MM4 guidelines. Testing with more laboratories and more lots is planned.

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Introduction

WCK 4282 (tazobactam-cefepime) is a novel antibacterial combination consisting of the β-lactamase inhibitor tazobactam combined with the fourth-generation cephalosporin cefepime. It has demonstrated excellent antibacterial activity against contemporary Gram-negative bacteria and existing isolates in synergy to existing drug classes. A Clinical and Laboratory Standards Institute (CLSI) M100-s26 (tier 2) quality control (QC) study was performed to establish disk diffusion QC ranges for cefepime-tazobactam (30/20 µg disk) against five reference bacterial strains to establish each of the QC reference strains. Among the three lots of MH agar tested, median zone diameters were 26.0 mm for E. coli ATCC 29213, 27.0 mm for P. aeruginosa ATCC 27853, 21.2 mm for E. coli NCTC 13353, 27.2 mm for S. aureus ATCC 29213, and 21.7 mm for S. aureus ATCC 25923. Ten replicates of each QC strain were tested using three different lot numbers of MH agar and two cefepime-tazobactam (30/20 µg) disks obtained from two separate manufacturers in eight distinct laboratories generating 450 zone diameters for each QC reference strain. Similarly, a total of 240 zone diameters were generated for each of the cefepime-tazobactam control disks against each of the QC reference strains.

Methods

Participating institutions: A total of eight laboratories participated in the CLSI M2-A4 QC study and provided results for WCK 4282 (cefepime-tazobactam) disk diffusion data for the five QC reference strains, as follows: JMI Laboratories, North Liberty, Iowa, USA (R.N. Jones, M.D., G. Denys, Ph.D., C. Hinton, M.D., and B. Huband), Merck & Co., Inc., Sharpstown, Philadelphia, Pennsylvania, USA (E. Munson, Ph.D.).

Quality control (QC) testing: Disk diffusion susceptibility testing was conducted using three lots of Mueller-Hinton (MH) agar plates produced by HiMedia Laboratories (Santa Margarita, California, USA), BBL (Becton Dickinson; Franklin Lakes, New Jersey, USA), and BD (Becton Dickinson, Franklin Lakes, New Jersey, USA). Each method was performed using 14 different lots of MH-Ag showing the same results.

Figure 1. Cefepime-tazobactam Zone Diameters for Medium Lot B (E. coli ATCC 25923) vs. Control Parameters

Table 1. Proposed/Approved CLSI quality control ranges for WCK 4282 (cefepime-tazobactam) 30/20 µg disk diffusion testing

Table 2. Proportion of control parameters in the approved CLSI ranges

Conclusions

• WCK 4282 disks (30/20 µg) disk diffusion susceptibility testing demonstrated accurate and reproducible results with the following CLSI QC ranges: E. coli ATCC 29213, 22.0 to 33.0 mm; E. coli ATCC 29222 and K. pneumoniae ATCC 700602, 29.0 to 36.0 mm; and P. aeruginosa ATCC 27853, 23.0 to 35.0 mm.

• Good intra- and inter-laboratory reproducibility was also observed for cefepime and cefepime-tazobactam disk diffusion against all QC reference strains.

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References

