

4-1-2018

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Diagnostic Microbiology and Infectious Disease, Vol. 90, No. 4 (April, 2018): 324-328. [DOI](#). This article is © Elsevier and permission has been granted for this version to appear in [e-Publications@Marquette](#). Elsevier does not grant permission for this article to be further copied/distributed or hosted elsewhere without the express permission from Elsevier.

Determination of MIC and Disk Diffusion Quality Control Guidelines for Meropenem–Vaborbactam, a Novel Carbapenem/Boronic Acid β -lactamase Inhibitor Combination

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Abstract

Meropenem–vaborbactam is a carbapenem/cyclic boronic acid [β-lactamase inhibitor](#) combination primarily active against [Gram-negative bacilli](#), including those harboring class A [serine](#) carbapenemases such as [Klebsiella pneumoniae carbapenemase](#) (KPC). A Clinical and Laboratory Standards Institute M23-A4 (Tier 2) quality control study established broth microdilution and disk diffusion ranges for reference strains. Two KPC-producing [K. pneumoniae](#) ATCC strains are recommended for quality control testing.

Keywords

Meropenem–vaborbactam, VABOMERE™, RPX7009, Quality control, CLSI M23

1. Introduction

The significance of multidrug-resistant [Enterobacteriaceae](#) to clinical medicine has been well documented, particularly in terms of disease incidence rates and association with poor clinical outcomes ([Thaden et al., 2017](#)). Carbapenem-resistant Enterobacteriaceae (CRE) are viewed as an urgent threat in this context ([CDC, 2013](#)) because rates of these infections have increased globally ([Sievert et al., 2013](#), [van Duijn et al., 2011](#)), invasive infections with CRE are associated with significant mortality ([Tzouveleakis et al., 2012](#)), and options to treat these organisms have become limited ([Thaden et al., 2017](#)). Vaborbactam (formerly RPX7009) is a cyclic boronic acid [β-lactamase inhibitor](#) designed to inactivate class A [serine](#) carbapenemases such as [Klebsiella pneumoniae carbapenemase](#) (KPC) ([Hecker et al., 2015](#)). [Castanheira et al. \(2016\)](#) reported that vaborbactam restored [meropenem](#) activity against a majority of KPC-producing isolates (optimally at a concentration of 8 µg/mL). This agent was well tolerated in a phase 1 healthy-volunteer study ([Griffith et al., 2016](#), [Wenzler et al., 2015](#)). A fixed-dose meropenem–vaborbactam product has completed phase 3 clinical trials for the treatment of complicated [urinary tract infection](#) (including acute pyelonephritis) and serious infection due to CRE ([ClinicalTrials.gov, 2016](#), [ClinicalTrials.gov, 2017](#)). The formulation is now FDA-approved for treatment of adult patients with complicated urinary tract infection, including pyelonephritis, caused by selected Enterobacteriaceae.

This investigation established broth microdilution and disk diffusion meropenem and meropenem–vaborbactam quality control (QC) ranges for Clinical and Laboratory Standards Institute (CLSI) reference strains of [Gram-positive](#) cocci and [Gram-negative bacilli](#). The addition of two KPC-producing [K. pneumoniae](#) reference strains [ATCC BAA-1705 (KPC-2, SHV) and ATCC BAA-2814 (KPC-3, SHV-11, TEM-1)] allows for QC of meropenem both alone and in combination with fixed concentration vaborbactam using different parts of the susceptibility dilution range. Meropenem–vaborbactam (VABOMERE™) recently received FDA approval for the treatment of complicated urinary tract infection ([VABOMERE™, 2017](#)). Broth microdilution and disk diffusion QC ranges for meropenem–vaborbactam will assist both clinical and reference laboratories in generating accurate susceptibility testing results in [clinical microbiology](#) practice.

2. Materials and Methods

Quality control investigations were designed using CLSI M23-A4 guidelines ([CLSI, 2016](#)) for Tier 2 studies. Frozen-form broth microdilution susceptibility panels containing meropenem–vaborbactam (testing range 0.004/8–8/8 µg/mL) and [meropenem](#) (testing range 0.125–256 µg/mL) were prepared at TREK Diagnostics/ThermoFisher Scientific (Oakwood Village, OH). Initial testing included [Escherichia coli](#) ATCC 25922 and ATCC 35218, [K. pneumoniae](#) ATCC 700603, [Pseudomonas aeruginosa](#) ATCC 27853, and [Staphylococcus aureus](#) ATCC 29213 using [Mueller–Hinton](#) broth (MHB) acquired from Becton Dickinson (BD; Sparks, MD; lot 2089488), Difco (Detroit, MI; lot 2080123), and Oxoid (Hampshire, United Kingdom; lot 1119455). Subsequent testing included KPC-producing reference strains (*K. pneumoniae* ATCC BAA-1705 and ATCC BAA-2814) and MHB lots obtained from BD (4293655), Difco (4196913), and Oxoid (1433705). Meropenem and vaborbactam powders were provided by The Medicines Company (Parsippany, NJ). All susceptibility testing and the majority of QC range determinations followed CLSI guidelines ([CLSI, 2015](#), [CLSI, 2016](#)). In certain scenarios, these determinations were supplemented with data derived from the RangeFinder statistical program ([Turnidge and Bordash, 2007](#)), which utilizes mean, median, and modal values to identify outliers.

Meropenem–vaborbactam and meropenem MIC values were obtained over a minimum of 3 days by 8 independent laboratories, generating 1 MIC value per strain/medium lot for 10 replicates (240 total MIC values per reference strain and test compound). [Inoculum](#) assessment yielded mean colony counts ranging from 2.9×10^5 (*K. pneumoniae* ATCC 700603) to 4.5×10^5 CFU/mL (*P. aeruginosa* ATCC 27853). Internal quality assurance for frozen panels included analysis of *P. aeruginosa* ATCC 27853 against meropenem (nine replicates per laboratory) and [piperacillin–tazobactam](#) (testing range 0.06/4–32/4 µg/mL; six replicates per laboratory).

For disk diffusion testing, individual lots of meropenem–vaborbactam disks (20/10 µg) were obtained from Bio-Rad Laboratories (Hercules, CA; lot 5H0011) and the MAST Group (Bootle, Merseyside, United Kingdom; lot 357368). Mueller–Hinton agar (MHA) was obtained from Hardy Diagnostics (Santa Maria, CA; lot H11-15302), ThermoFisher (Lenexa, Ks; lot 766782), and BBL (Sparks, MD; lot 5287893). Susceptibility testing and disk diffusion QC range determinations followed CLSI guidelines ([CLSI, 2015](#), [CLSI, 2016](#)). Meropenem–vaborbactam disk zone diameters against *E. coli* ATCC 25922; *K. pneumoniae* ATCC 700603, ATCC BAA-1705, and ATCC BAA-2814; *P. aeruginosa* ATCC 27853; and *S. aureus* ATCC 25923 were obtained by 7 laboratories over a minimum interval of 3 days, generating 1 zone diameter value per reference strain/disk lot/medium lot for 10 replicates (420 total zone diameter values per reference strain and test compound). Internal quality assurance included analysis of selected strains against 10 µg meropenem (BD lot 5147624) and 100/10 µg piperacillin–tazobactam disks (BD lot 5111769; 30 replicates per laboratory).

3. Results and Discussion

Broth microdilution quality assurance testing demonstrated that 98.8% of [meropenem](#) and 100.0% of [piperacillin–tazobactam](#) MIC values for *P. aeruginosa* ATCC 27853 were within QC ranges published in the CLSI M100-S27 ([CLSI, 2017](#)) document (data not shown). Three log₂-dilution meropenem–vaborbactam QC ranges were characterized for *S. aureus* ATCC 29213 (0.03/8–0.12/8 µg/mL) and *K. pneumoniae* ATCC 700603 (0.015/8–0.06/8 µg/mL), accounting for ≥97.1% of all MIC values ([Table 1](#)). On the basis of CLSI M23-A4 criteria and bimodal MIC distributions, four log₂-dilution meropenem–vaborbactam QC ranges were calculated for *E. coli* ATCC 25922 (0.008/8–0.06/8 µg/mL), *E. coli* ATCC 35218 (0.008/8–0.06/8 µg/mL), and *P. aeruginosa* ATCC 27853 (0.12/8–1/8 µg/mL), encompassing 100.0% of all MIC values. Susceptibility shoulders were noted within these three strains representing 72.0%, 60.0%, and 65.3% of the modal meropenem–vaborbactam MIC values, respectively. With respect to *E. coli* ATCC 35218, RangeFinder calculated a three log₂-dilution QC range of 0.015/8–0.06/8 µg/mL, encompassing 98.3% of meropenem–vaborbactam MIC values.

Table 1. CLSI-approved broth microdilution and disk diffusion zone diameter quality control ranges for meropenem–vaborbactam and [meropenem](#).

QC reference strain	MIC range (µg/mL) (% in range)		Zone diameter range (mm) (% in range)	
	Meropenem–vaborbactam	Meropenem	Meropenem–vaborbactam (20/10 µg)	Meropenem (10 µg)
<i>S. aureus</i> ATCC 29213	0.03/8–0.12/8 (100.0%)	0.03–0.12 ^b (100.0%)	-- ^a	-- ^a
<i>S. aureus</i> ATCC 25923	-- ^a	-- ^a	32–38 (97.6%)	29–37 ^b (100.0%)
<i>E. coli</i> ATCC 25922	0.008/8–0.06/8 (100.0%)	0.008–0.06 ^b (100.0%)	31–37 (99.0%)	28–35 (100.0%)
<i>Escherichia coli</i> ATCC 35218	0.008/8–0.06/8 (100.0%)	-- ^a	-- ^a	-- ^a
<i>K. pneumoniae</i> ATCC 700603	0.015/8–0.06/8 (99.6%)	-- ^a	29–35 (99.3%)	no range
<i>K. pneumoniae</i> ATCC BAA-1705	0.008/8–0.06/8 (99.6%)	8–64 (95.8%)	21–27 (100.0%)	11–18 ^c (99.5%)
<i>K. pneumoniae</i> ATCC BAA-2814	0.12/8–0.5/8 (98.3%)	32–256 (100.0%)	16–20 (100.0%)	6 ^c (100.0%)
<i>P. aeruginosa</i> ATCC 27853	0.12/8–1/8 (100.0%)	0.12–1 ^b (96.3%)	29–35 (99.3%)	27–33 ^b (99.5%)

a --, no proposed range.

b Previously approved CLSI QC range for meropenem.

c QC range established using meropenem zone diameter data from one manufacturer.

K. pneumoniae ATCC BAA-1705 and ATCC BAA-2814 were investigated as potential QC reference strains as the currently available strains could not adequately QC the activity of the meropenem–vaborbactam combination over meropenem alone. In addition, *K. pneumoniae* ATCC BAA-1705 and ATCC BAA-2814 allow for the QC of different portions of the

meropenem–vaborbactam QC range. With respect to meropenem–vaborbactam, CLSI M23-A4 criteria and RangeFinder both calculated a three log₂-dilution QC range of 0.12/8–0.5/8 µg/mL for *K. pneumoniae* ATCC 2814 (Fig. 1), encompassing 98.3% of MIC values. For *K. pneumoniae* ATCC BAA-1705, the meropenem–vaborbactam modal MIC value of 0.015/8 µg/mL demonstrated a 67.7% shoulder at 0.03 µg/mL, supporting a four log₂-dilution QC range of 0.008/8–0.06/8 µg/mL (Fig. 1). These data were corroborated by RangeFinder and included 99.6% of meropenem–vaborbactam MIC values. Individual MHB lots incorporated into meropenem–vaborbactam QC range determination resulted in between 88.8% and 96.3% of *K. pneumoniae* ATCC BAA-1705 MIC values recorded at 0.015/8 or 0.03/8 µg/mL. Similarly, analysis of *K. pneumoniae* ATCC BAA-2814 meropenem–vaborbactam data revealed that, irrespective of MHB lot, 97.5% to 98.8% of MIC values fell between 0.12/8 and 0.5/8 µg/mL.

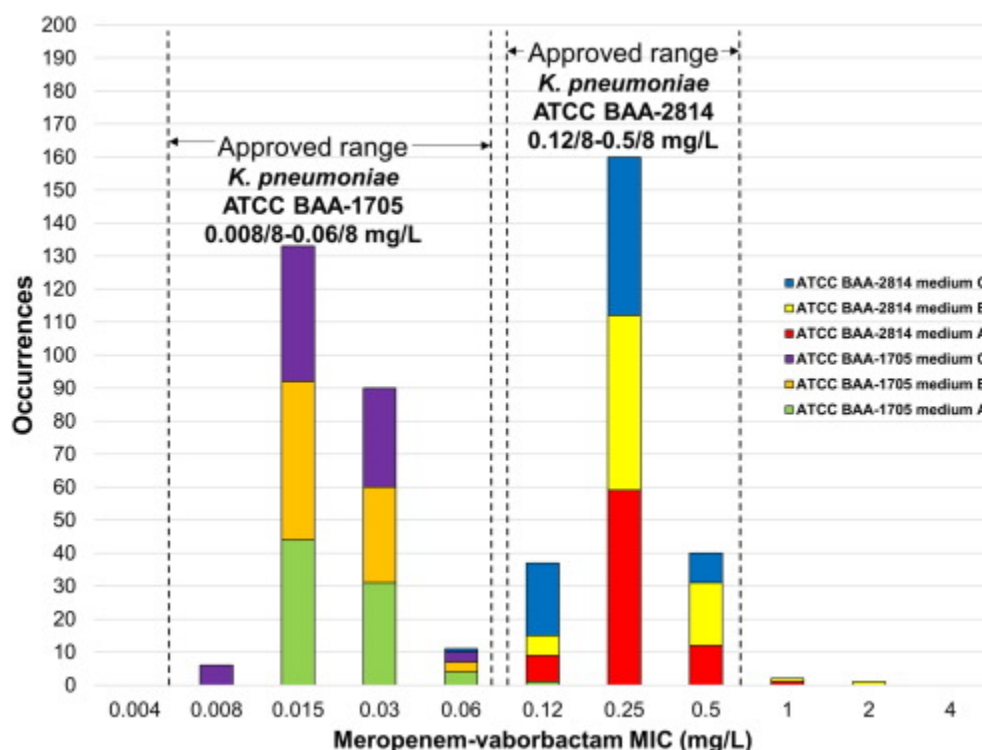


Fig. 1. CLSI-approved broth microdilution meropenem–vaborbactam (fixed 8 µg/mL) MIC distributions by medium lot for *K. pneumoniae* ATCC BAA-1705 (KPC-2) and *K. pneumoniae* ATCC BAA-2814 (KPC-3). Medium lot A is Becton Dickinson, medium lot B is Difco, and medium lot C is Oxoid.

A bimodal distribution of meropenem MIC values against *K. pneumoniae* ATCC BAA-2814 was observed (Fig. 2), indicating a four log₂-dilution QC range of 32–256 µg/mL that included 100.0% of all MIC values. With respect to *K. pneumoniae* ATCC BAA-1705, a four log₂-dilution QC range of 8–64 µg/mL including 95.8% of all meropenem MIC values was proposed using CLSI M23-A4 criteria and RangeFinder results (Fig. 2).

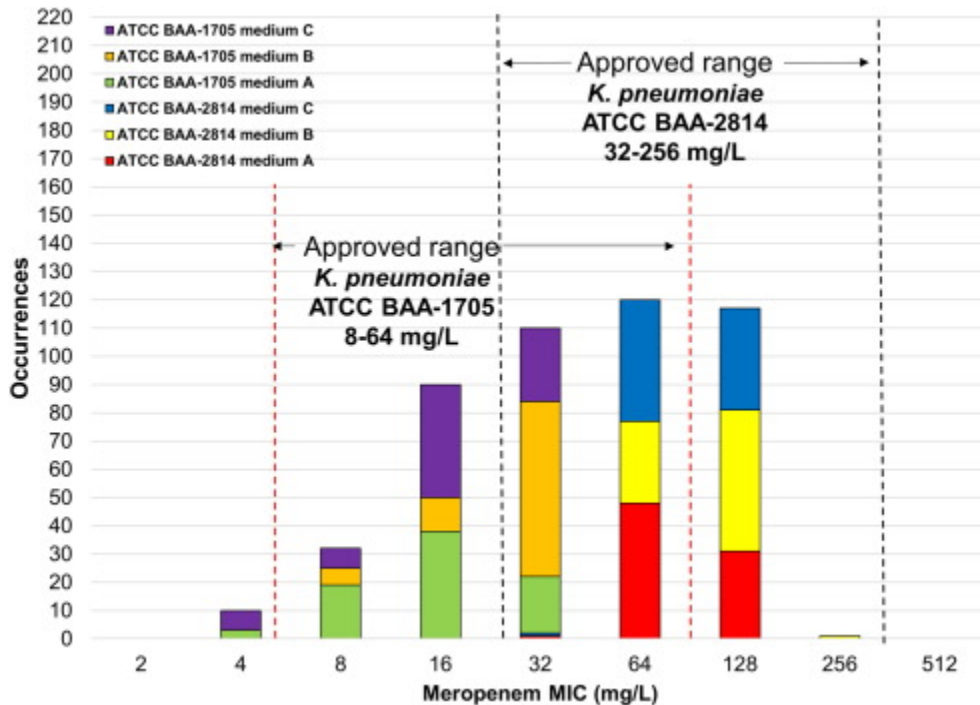


Fig. 2. CLSI approved broth microdilution [meropenem](#) MIC distributions by medium lot for [K. pneumoniae](#) ATCC BAA-1705 (KPC-2) and [K. pneumoniae](#) ATCC BAA-2814 (KPC-3). Medium lot A is Becton Dickinson, medium lot B is Difco, and medium lot C is Oxoid.

Disk diffusion quality assurance demonstrated 99.8% and 100.0% of meropenem and piperacillin-tazobactam zone diameters, respectively, within CLSI-published QC ranges ([CLSI, 2017](#)). The results of two laboratories were identified by RangeFinder as statistical outliers for their modal meropenem zone diameter values for *S. aureus* ATCC 25923. One laboratory was identified by RangeFinder as a statistical outlier for the modal meropenem MIC value against *P. aeruginosa* ATCC 27853, and another laboratory was identified as a statistical outlier for the meropenem MIC value against *K. pneumoniae* ATCC 700603. The results of two laboratories were based on modal meropenem–vaborbactam zone diameter outliers for *S. aureus* ATCC 25923. The aforementioned laboratories were not excluded from subsequent analysis, as the mean and median zone diameter values (as calculated by RangeFinder) were within acceptable limits. Meropenem–vaborbactam 20/10- μ g disks produced by Bio-Rad yielded slightly larger zone diameters (geometric mean difference between 0.1 and 1 mm) than disks produced by MAST.

With respect to a 20/10- μ g meropenem–vaborbactam disk, zone diameter QC ranges of 32–38 mm for *S. aureus* ATCC 25923 (encompassing 97.6% of zone diameter values), 31–37 mm for *E. coli* ATCC 25922 (including 99.0% of zone diameter values), and 29–35 mm for both *K. pneumoniae* ATCC 700603 and *P. aeruginosa* ATCC 27853 (99.3% of zone diameter values inclusive in both instances) were proposed ([Table 1](#)). These zone diameter values were derived from calculation of the 95% confidence interval around the mean ([CLSI, 2016](#)). RangeFinder corroborated all findings, with the exception of a larger proposed range for *S. aureus* ATCC 25923 (31–39 mm) that encompassed 99.8% of zone diameter values. For a 10- μ g meropenem control disk, zone diameter QC ranges of 29–37 mm for *S. aureus* ATCC

25923 and 27–33 mm for *P. aeruginosa* ATCC 27853 included 100.0% and 99.5% of all zone diameter values, respectively. Of note, the previously approved meropenem disk diffusion QC range of 28–34 mm for *E. coli* ATCC 25922 (encompassing 100.0% of zone diameter values; [Table 1](#)) was revised to 28–35 mm based on the outcome of this multilaboratory QC study ([CLSI, 2017](#)).

In further studies to identify relevant carbapenem/ β -lactamase inhibitor QC strains, a meropenem–vaborbactam disk diffusion QC range of 21–27 mm for *K. pneumoniae* ATCC BAA-1705 was determined ([Fig. 3](#)). Alternatively, a RangeFinder zone diameter QC range of 22–27 mm included 100.0% of results. No skewing was observed with respect to lot of MHA used.

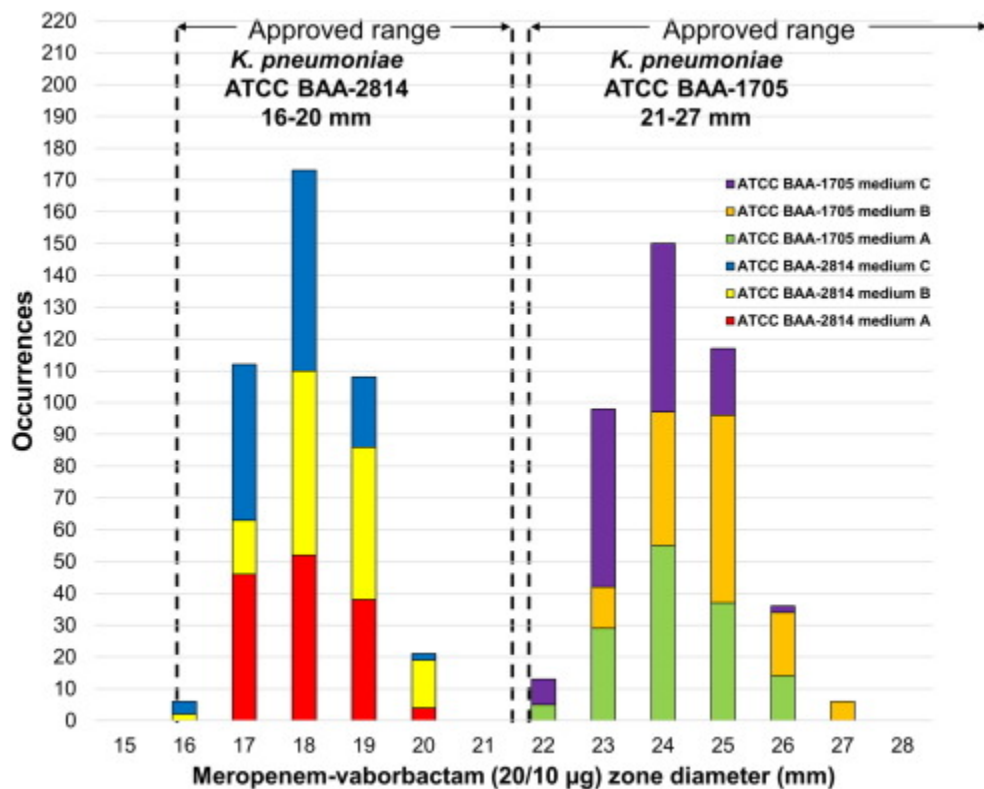


Fig. 3. CLSI-approved disk diffusion meropenem–vaborbactam (20/10 μ g) zone diameter distributions by medium lot for *K. pneumoniae* ATCC BAA-1705 (KPC-2) and *K. pneumoniae* ATCC BAA-2814 (KPC-3). Medium lot A is Remel, medium lot B is Hardy Diagnostics, and medium lot C is BBL.

A CLSI-derived meropenem zone diameter range of 12–18 mm included 96.2% of all zone diameter values, while a zone diameter QC range of 11–18 mm, as determined by RangeFinder ([Fig. 4](#)), captured 99.5% of zone diameter values. However, this meropenem analysis was limited by single-lot disk testing. For *K. pneumoniae* ATCC BAA-2814, a CLSI M23-A4 zone diameter QC range of 16–20 mm for meropenem–vaborbactam (20/10 μ g) included all zone diameter values ([Fig. 3](#)). All *K. pneumoniae* ATCC BAA-2814 replicates demonstrated no meropenem inhibition zone (6 mm; single-lot disk testing), confirming the carbapenem-resistant nature of this strain. These data, as well as MIC findings ([Fig. 1](#), [Fig. 2](#)), ascribe value to both *K. pneumoniae* ATCC BAA-1705 and ATCC BAA-2814 as QC reference

strains confirming both the [antibacterial activity](#) of meropenem and demonstrating the [β-lactamase inhibitor](#) activity of vaborbactam.

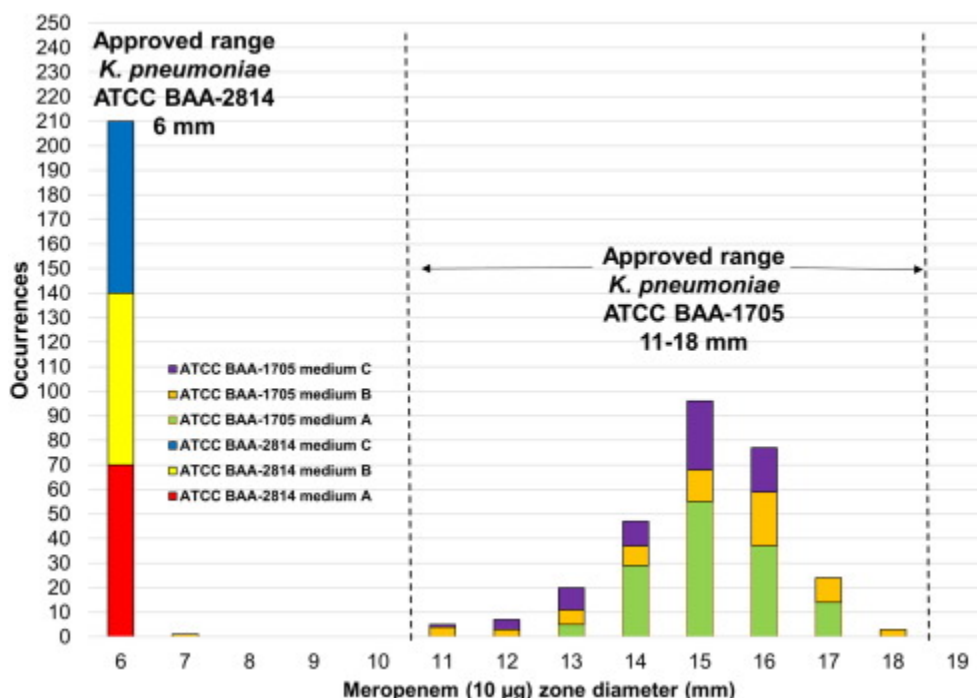


Fig. 4. CLSI-approved disk diffusion [meropenem](#) (10 µg) zone diameter distributions by medium lot for [K. pneumoniae](#) ATCC BAA-1705 (KPC-2) and [K. pneumoniae](#) ATCC BAA-2814 (KPC-3). Medium lot A is Remel, medium lot B is Hardy Diagnostics, and medium lot C is BBL.

The CLSI Subcommittee on [Antimicrobial](#) Susceptibility Testing approved the proposed meropenem and meropenem–vaborbactam MIC QC ranges ([Table 1](#)) for *E. coli* ATCC 25922 and 35218, *K. pneumoniae* ATCC 700603, *P. aeruginosa* ATCC 27853, and *S. aureus* ATCC 29213 in January 2015. Disk diffusion QC ranges for *E. coli* ATCC 25922; *K. pneumoniae* ATCC 700603, ATCC BAA-1705, and ATCC BAA-2814; *P. aeruginosa* ATCC 27853; and *S. aureus* ATCC 25923 were approved in June 2016. MIC QC ranges for *K. pneumoniae* ATCC BAA-1705 and ATCC BAA-2814 were approved in January 2017 after publication of the CLSI M100-S27 document. Values listed in [Table 1](#) also reflect those listed in the FDA-approved formulation of meropenem–vaborbactam ([VABOMERE™, 2017](#)), with the exception of the revised MIC QC range for *K. pneumoniae* ATCC BAA-1705 and the newly approved MIC QC range for *K. pneumoniae* ATCC BAA-2814. *K. pneumoniae* ATCC BAA-1705 and/or *K. pneumoniae* ATCC BAA-2814 should be used as QC reference strains when evaluating the activity of meropenem–vaborbactam combinations as they provide QC on both the meropenem and vaborbactam components of the antimicrobial combination.

Acknowledgments

This study was funded by a research grant from The Medicines Company.

Participants in various facets of these studies included: JMI Laboratories, North Liberty, IA (M. Castanheira); ThermoFisher Scientific, Cleveland, OH (C. Knapp); University of Rochester Medical Center, Rochester, NY (D. Hardy); Indiana University Health/Methodist Hospital, Indianapolis, IN (G. Denys); University of Alberta Hospitals, Edmonton, Alberta, Canada (R. Rennie); Summa Health Systems, Akron, OH (G. Kallstrom); Marquette University, Milwaukee, WI (E. Munson); Marshfield Laboratories, Marshfield, WI (broth microdilution only, T. Fritsche); Micromyx Incorporated, Kalamazoo, MI (broth microdilution only, C. Pillar); Cleveland Clinic, Cleveland, OH (broth microdilution only, G. Procop); University of Washington Medical Center, Seattle, WA (broth microdilution only, S. Swanzy); and Johns Hopkins Bayview Medical Center, Baltimore, MD (broth microdilution only, S. Riedel).

JMI Laboratories, Inc., was contracted to perform services in 2016 for Achaogen, Actelion, Allegra, Allergan, Ampliphi, API, Astellas, AstraZeneca, Basilea, Bayer, BD, Biomodels, Cardeas, CEM-102 Pharma, Cempra, Cidara, Cormedix, CSA Biotech, Cubist, Debiopharm, Dipexium, Duke, Durata, Entasis, Fortress, Fox Chase Chemical, GSK, Medpace, Melinta, Merck, Micurx, Motif, N8 Medical, Nabriva, Nexcida, Novartis, Paratek, Pfizer, Polyphor, Rempex, Scynexis, Shionogi, Spero Therapeutics, Symbal Therapeutics, Synolgoic, TGV Therapeutics, Theravance, ThermoFisher, Venatorx, Wockhardt, and Zavante. Some JMI employees are advisors/consultants for Allergan, Astellas, Cubist, Pfizer, Cempra, and Theravance. There are no speakers' bureaus or stock options to declare.

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