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An FDA-Approved Study for an AST Disc 510(k) Submission: Comparison of a Thermo Scientific Oxoid AST Disc to a Predicate AST Disk for Meropenem-Vaborbactam

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ABSTRACT

An evaluation was designed to determine the accuracy and reproducibility of the new Thermo Fisher™ Oxoid™ Antimicrobial Susceptibility Testing Disc against a predicate device, the Meropenem-Vaborbactam HardyDisk™ (Hardy Diagnostics, Santa Maria, CA). Due to recent changes in the FDA requirements for AST Disk 510(K) submissions, this is the first study of its kind to be accepted by the FDA, setting a precedent for future submissions from AST manufacturers. VABOMERE® (Melinta Therapeutics, Morristown, NJ), a combination of meropenem and vaborbactam, is indicated for the treatment of patients 18 years of age and older with complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganisms: *Escherichia coli, Klebsiella pneumoniae and Enterobacter cloacae species complex*.

Two lots of investigational use only Oxoid meropenem-vaborbactam disks provided by Thermo Fisher were tested with 375 (300 clinical + 75 challenge) isolates using Clinical and Laboratory Standards Institute (CLSI) M02-A13 (2018) method[1] with FDA-cleared Mueller Hinton agar (MHA). One lot of commercial Hardy (Mast Group Ltd.) meropenem-vaborbactam disks were tested in comparison. Thermo Scientific™ Remel™ MHA supplied by Thermo Fisher was used for all testing. Quality Control (QC) was carried out daily as per CLSI M02-A13[1] and M100-S28[2] documents using American Type Culture Collection (ATCC) strains.

The results from the comparative study indicate that the Oxoid disc performs accurately and reliably. The FDA have determined that the performance of the Oxoid disc was equivalent to the predicate device.

INTRODUCTION

Until recently, 510(k) submissions for AST disks that had not been evaluated by CDER (the Center for Drug Evaluation and Research, part of the FDA) as part of a drug submission did not require clinical performance data to be submitted. The FDA now require clinical evidence to demonstrate acceptable performance of the device. However, there is currently no guidance document available for disk manufacturers to assist with designing a suitable study. Along with JMI Laboratories (North Liberty,IA) and Melinta Therapeutics, we worked with the FDA using the pre-submission process to produce a study which was deemed acceptable to demonstrate the clinical performance of the disk. Future disk 510(k) submissions should now be able to use the same approach and gain more rapid agreement from the FDA as to the suitability of the new studies when they are proposed. The purpose of the study presented here was to demonstrate the equivalence of the new Oxoid meropenem-vaborbactam Disc (20 µg/10 µg) to the cleared predicate device Hardy meropenem-vaborbactam disk (20 µg/10 µg). This involved testing of 300 clinical isolates from previous treatment trials, 75 challenge isolates and 15 reproducibility isolates.

MATERIALS AND METHODS

In a single lab study, 300 clinical trial isolates, chosen from 2 meropenem-vaborbactam clinical trials with varying resistance phenotypes, were tested in 3 groups of 100 by three separate operators (to effectively represent 3 sites), with 2 disk batches (1 Hardy disk and 1 Oxoid disc). Seventy five challenge isolates were also tested with 2 disc batches (1 Hardy disk and 1 Oxoid disc). The Vabormere package label submitted to the FDA (2017) shows susceptibility interpretive criteria for the disk zone diameters as presented in Table 1. A summary of the total organisms tested is shown in Table 2.

Quality Control (QC) testing was carried out on both lots of Oxoid discs according to the CLSI M02-A13 (2018)[1] and M100-S28[2] documents using American Type Culture Collection (ATCC) strains. The QC strains and their approved zone size ranges are shown in Table 3. 22 replicates for each CLSI QC strain were tested by 3 readers. Fifteen reproducibility isolates were set up by 1 person on 3 separate days using 2 lots of Oxoid discs and 1 Hardy disk. The same MHA plate with 3 discs were read by three different readers each day. Each reader recorded their results separately and did not see other readers' results. A total of 270 values were collected for Oxoid discs (18 per isolate) and 135 values for the Hardy disk. Colony Counts were performed on the inoculums of the clinical, challenge, reproducibility and QC strains on each day of testing.

MATERIALS AND METHODS CONT.

Table 1. Susceptibility Interpretive Criteria for Meropenem-Vaborbactam Disk (30µg)

Pathogen	Disc Diffusion Zone Diameter (mm)		
	S	I	R
Enterobacteriaceae	≥17	14-16	≤13

Table 2. Total organisms tested

Organisms Tested	Number Tested
Clinical Isolates	300
Challenge Isolates	75
Reproducibility Isolates (3 readers on 3 days, 2 disk batches)	15 (270)
ATCC Quality Control Strains (22 replicates by 3 readers, 2 disk batches)	4 (528)
TOTAL	1173

Table 3. Quality Control Strains

Quality Control Strains	CLSI QC Ranges (mm)
Escherichia coli ATCC 25922	31 - 37
Klebsiella pneumoniae ATCC 700603	29 - 35
Klebsiella pneumoniae ATCC BAA-1705	21 - 27
Klebsiella pneumoniae ATCC BAA-2814	16 - 20

RESULTS

The results of the clinical, challenge, QC and reproducibility testing met the acceptance criteria defined by the FDA. These were in accordance with the AST Special Controls guidance[3]: Categorical Agreement of >89.9%, major discrepancy rate of ≤3% based on the number of susceptible isolates tested and very major discrepancy rate of ≤1.5% based on the number of resistant isolates tested.

The Categorical Agreement for the Oxoid disc with the predicate device for the 375 clinical and challenge isolates was 99.2%. One minor error was observed for each batch; there were no major or very major errors. A summary of the data is presented in Figures 1(a) and 1(b).

Reproducibility was calculated as the percent of results which were within plus or minus 3 mm of the modal value and a value of ≥95% was deemed acceptable. All data was shown to be 100% reproducible both within-reader and between-reader. The full data set is presented in Table 4.

The acceptance criteria for the QC results were for 95% to be within the approved range. QC results were within range 95.5% of the time for Oxoid disc batch A and 96.2% of the time for Oxoid disc batch B.

Figure 1 (a). Comparative performance data for Oxoid disc batch A

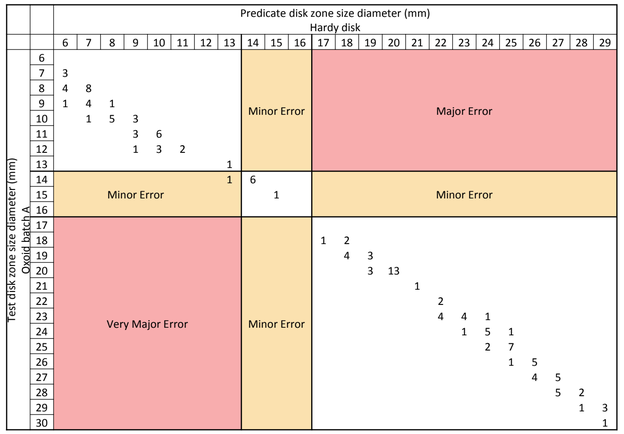

Figure 1 (b). Comparative performance data for Oxoid disc batch B

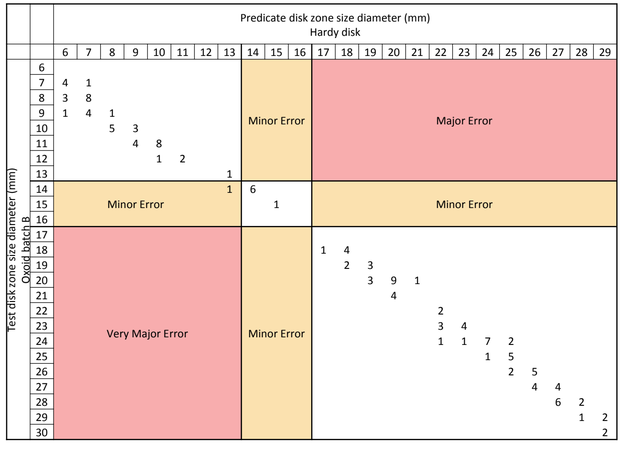

Table 4. Reproducibility data for Oxoid disc batches A and B

Organism	Difference in mm comparing test results with test mode										Test Mode/ Median (mm)
	>3 mm below test mode	-3	-2	-1	0	1	2	3	>3 mm above test mode		
Klebsiella pneumoniae (KP1446)				6	12						8
Klebsiella pneumoniae (KP1287)			1	5	7	3	2				24
Klebsiella pneumoniae (KP1234)				2	8	8					11
Klebsiella pneumoniae (KP1233)				4	13	1					11
Klebsiella pneumoniae (KP1099)				8	10						19
Klebsiella pneumoniae (KP1092)				2	14	2					14
Klebsiella pneumoniae (KP1087)				3	11	4					23
Klebsiella pneumoniae (KP1084)					14	4					20
Klebsiella pneumoniae (KP1070)				4	7	5	2				27
Klebsiella pneumoniae (KP1064)				2	15	1					20
Klebsiella pneumoniae (KP1015)			2	5	11						10
Klebsiella pneumoniae (KP1004)				7	9	2					25
Enterobacter cloacae (ECL1111)			3	5	6	4					27
Escherichia coli (EC1073)				2	9	7					8
Citrobacter freundii species complex (CF1012)				4	6	5	3				28
Total	0	0	6	59	152	46	7	0	0		
Reproducibility	**100% (270/270)**										

CONCLUSIONS

When compared with the HardyDisk, one minor error was observed for each batch of Oxoid discs; there were no major or very major errors. The categorical agreement for each batch was 99.26%. Reproducibility was calculated as the percent of results which were within plus or minus 3 mm of the modal value. All data was shown to be 100% reproducible both within-reader and between-reader. QC results were within range 96% of the time for each batch.

Based on the results from this study the FDA have determined that the performance of the Oxoid disc was equivalent to the predicate device and have cleared the product. The Oxoid disc was shown to perform accurately and reliably.

REFERENCES

1. Clinical and Laboratory Standards Institute. 2018. Performance Standards for Antimicrobial Disk Susceptibility Tests, 13th Edition. Approved document M02-A13. Wayne, PA: CLSI.

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3. FDA Guidance for Industry and FDA Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems, August 28, 2009.

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