Methodology Working Group

June 15, 2015

Methodology Group Membership

- Co-Chairs
  - Stephen Jenkins
  - Brandi Limbago
- Bill Brasso
- Romney Humphries
- Joe Kuti
- Sandra Richter
- Darcie Roe-Carpenter
- Katherine Sei
- Susan Sharp
- Ribhi Shawar
- John Turnidge
- Laura Koeth
- Tracy Dooley

Topics for Today's Session

1. Shionogi - Discuss methodologic path(s) forward for new drugs that aren't compatible with current reference methods
2. Cubist/Merck – Discuss and provide guidance to sponsor on the implications of text in CLSI document M07 regarding linezolid and trailing endpoints, to better understand the implications of this text since both tedizolid and linezolid are members of the oxazolidinone class.
3. The Medicines Company - Current developmental progress for oritavancin disk diffusion, focusing on use of a supplemental (alternative) QC isolate and selection of appropriate MHA. Also discuss with sponsor planning of an M23 Tier 2QC study for oritavancin disks that takes into consideration the points above.

The Medicines Company

- Presentation on current developmental progress for oritavancin disk diffusion, focusing on use of a supplemental (alternative) QC isolate and selection of appropriate MHA.
- Also, discuss with sponsor planning of an M23 Tier 2QC study for oritavancin disks that takes into consideration the points above

Methods WG Recommendations

- Disk as proposed should be used for testing of oritavancin (Oritavancin dissolved in a solution of Polysorbate 80 (P80)/Span 80 (S80))
- To use *S. aureus* ATCC 29213 as the QC isolate for oritavancin disk diffusion
- Add verbiage to Troubleshooting Table stating that Oritavancin disk diffusion is affected by source of Mueller-Hinton agar (MHA)

Vote: 9/0/0

MIC Endpoint Interpretation for TZD

CLSI June 2015

Current M7-A10 Text: Exclude Linezolid Trailing

Exceptions to reading complete inhibition of growth:

For gram-positive cocci when testing chloramphenicol, clindamycin, erythromycin, linezolid, and tetracycline, trailing growth can make end-point determination difficult.

In such cases, read the MIC at the first spot where the trailing begins. Tiny buttons of growth should be ignored (see Figures 3 and 4).

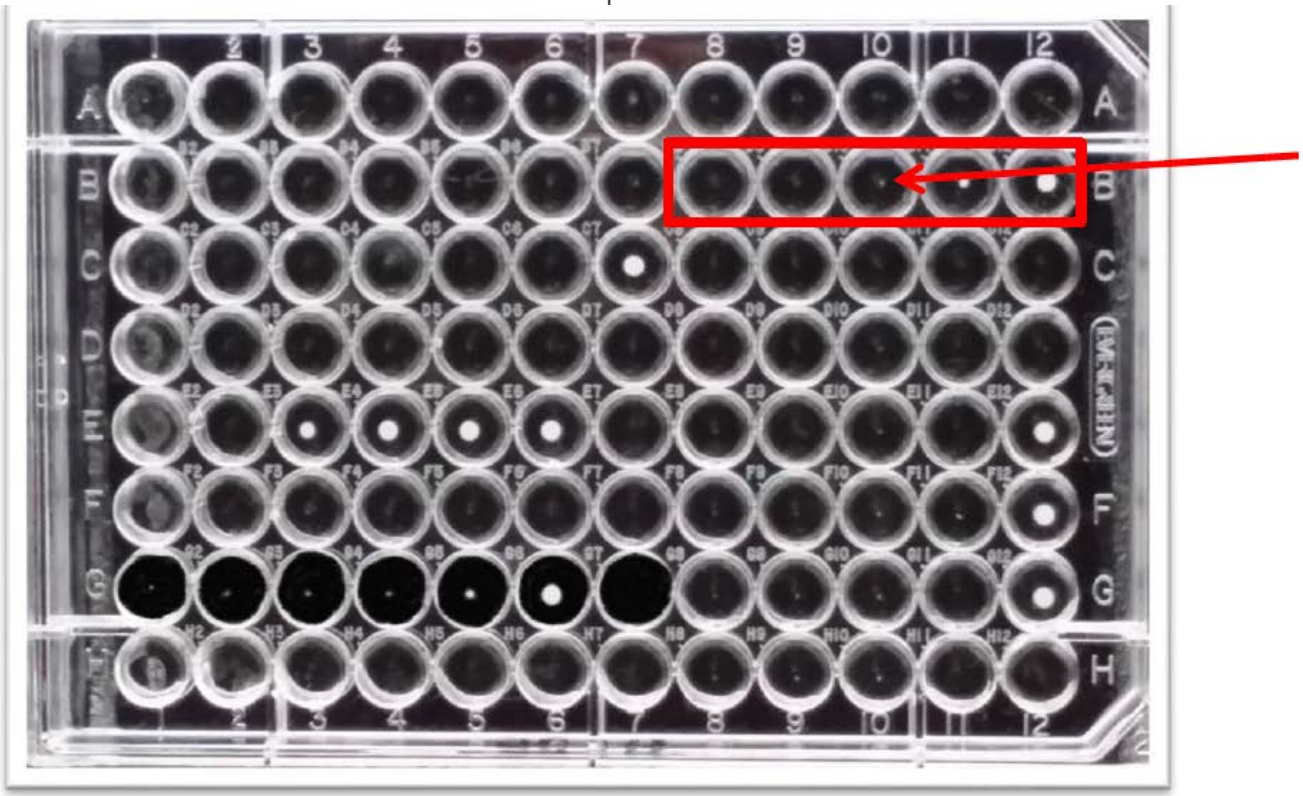


Figure 4. Linezolid: Trailing End Points (B8–B12, 16–1 µg/mL), MIC = B10

Proposed text for M7-A11 Text: Exclude Linezolid & Tedizolid Trailing

- Exceptions to reading complete inhibition of growth

For gram-positive cocci when testing chloramphenicol, clindamycin, erythromycin, linezolid, **tedizolid**, and tetracycline, trailing growth can make end-point determination determination difficult.

In such cases, read the MIC at the first spot where the trailing begins. Tiny buttons of growth should be ignored (see Figures 3 and 4).

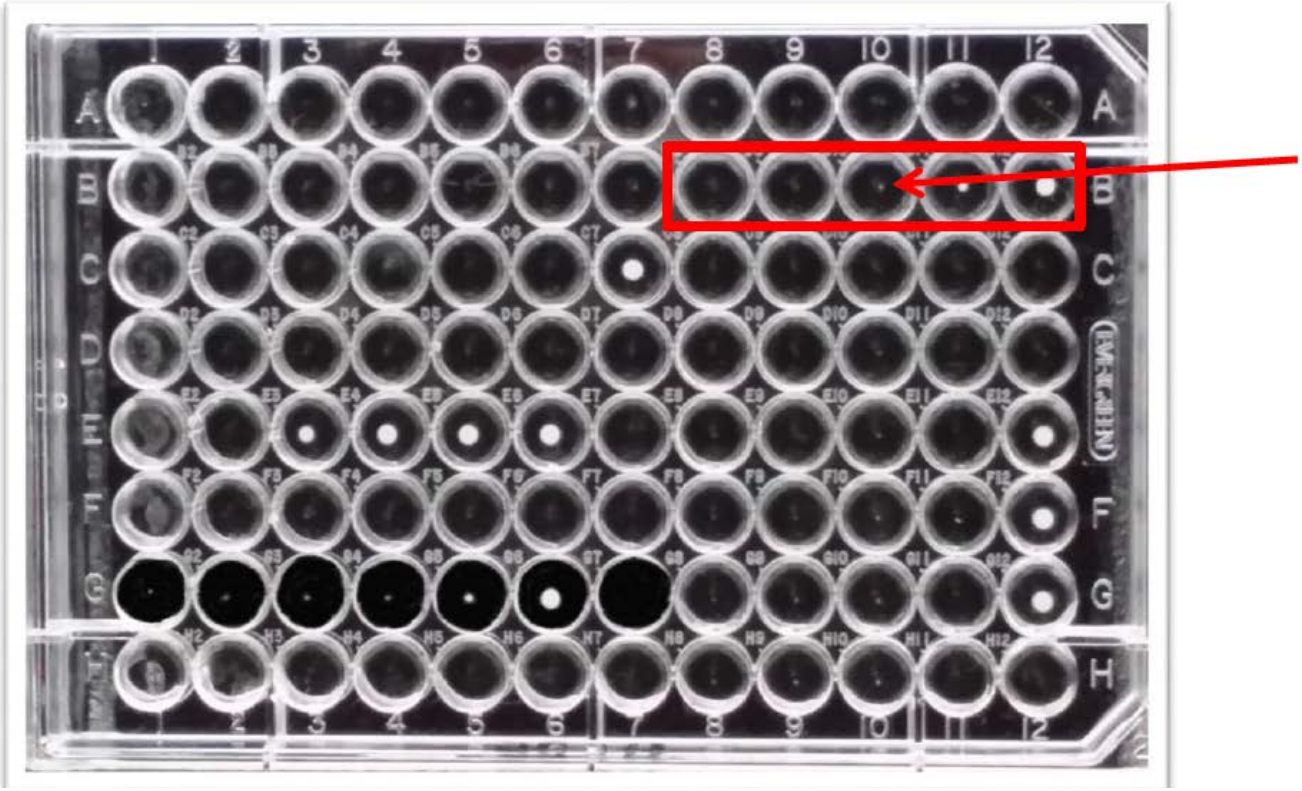


Figure 4. Linezolid **and tedizolid:** Trailing end Points B8-12, 16-1 µg/mL), MIC = B10

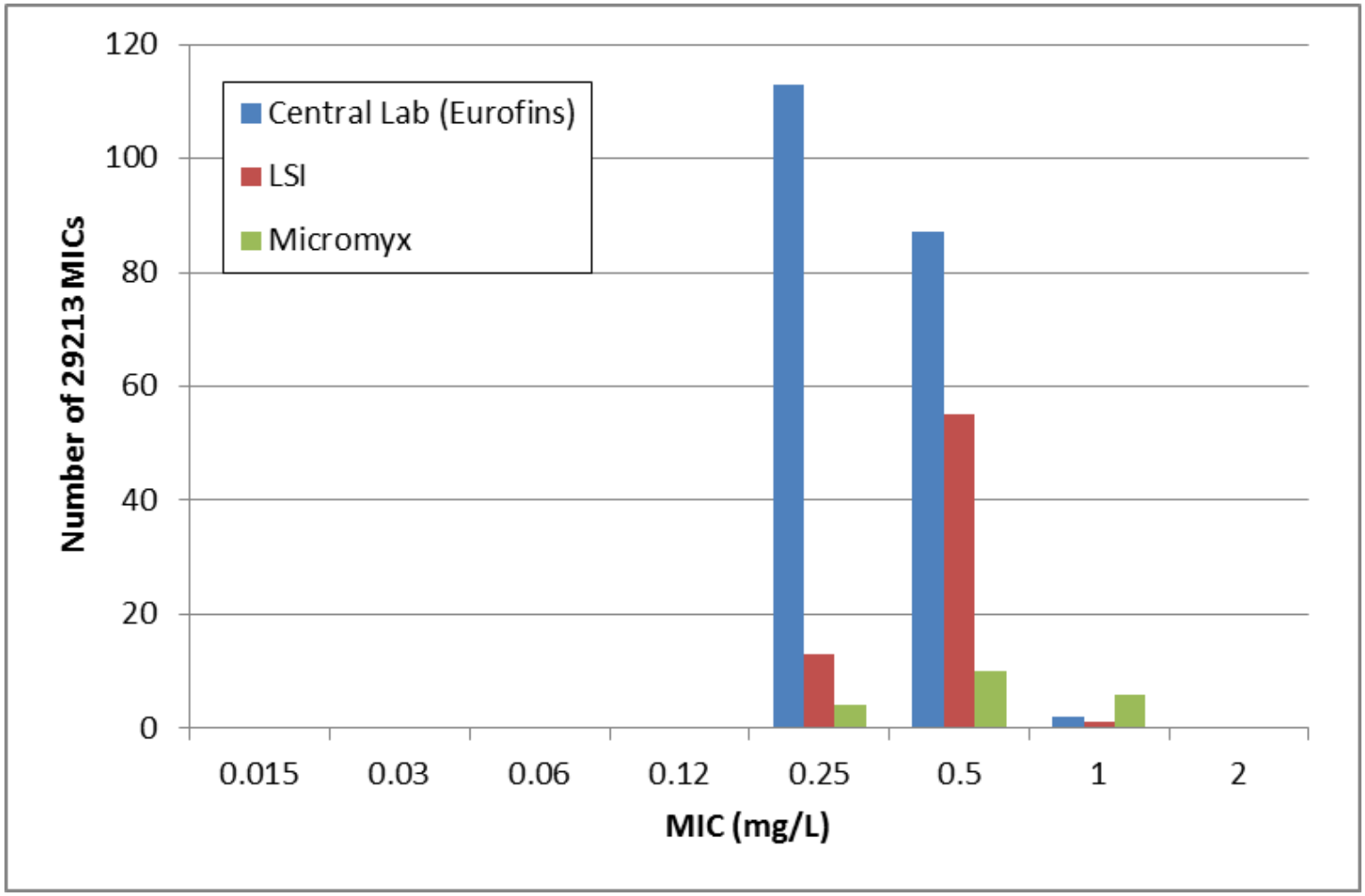
TZD QC study: variability b/w laboratories & media

S. aureus ATCC 29213

MIC (ug/ml)	Lot 1	Lot 2	Lot 3	Lab 1	Lab 2	Lab 3	Lab 4	Lab 5	Lab 6	Lab 7	Lab 8	All Labs
0.002												
0.004												
0.008												
0.015												
0.03												
0.06												
0.12												
0.25	25	16	11	7			1	3	30	11		52
0.5	45	51	53	23	29	6	29	26		19	17	149
1	10	13	14		1	22		1			13	37
2			2			2						2
4												
8												
16												
32												
64												

N	80	80	80	30	30	30	30	30	30	30	30	240
GEOMEAN	0.439	0.487	0.531	0.425	0.512	0.912	0.489	0.477	0.250	0.388	0.675	0.484
MODE	0.5	0.5	0.5	0.5	0.5	1	0.5	0.5	0.25	0.5	0.5	0.5
MIN	0.25	0.25	0.25	0.25	0.5	0.5	0.25	0.25	0.25	0.25	0.5	0.25
MAX	1	1	2	1	1	2	0.5	1	0.25	0.5	1	2
RANGE	3	3	4	2	2	3	2	3	1	2	2	4

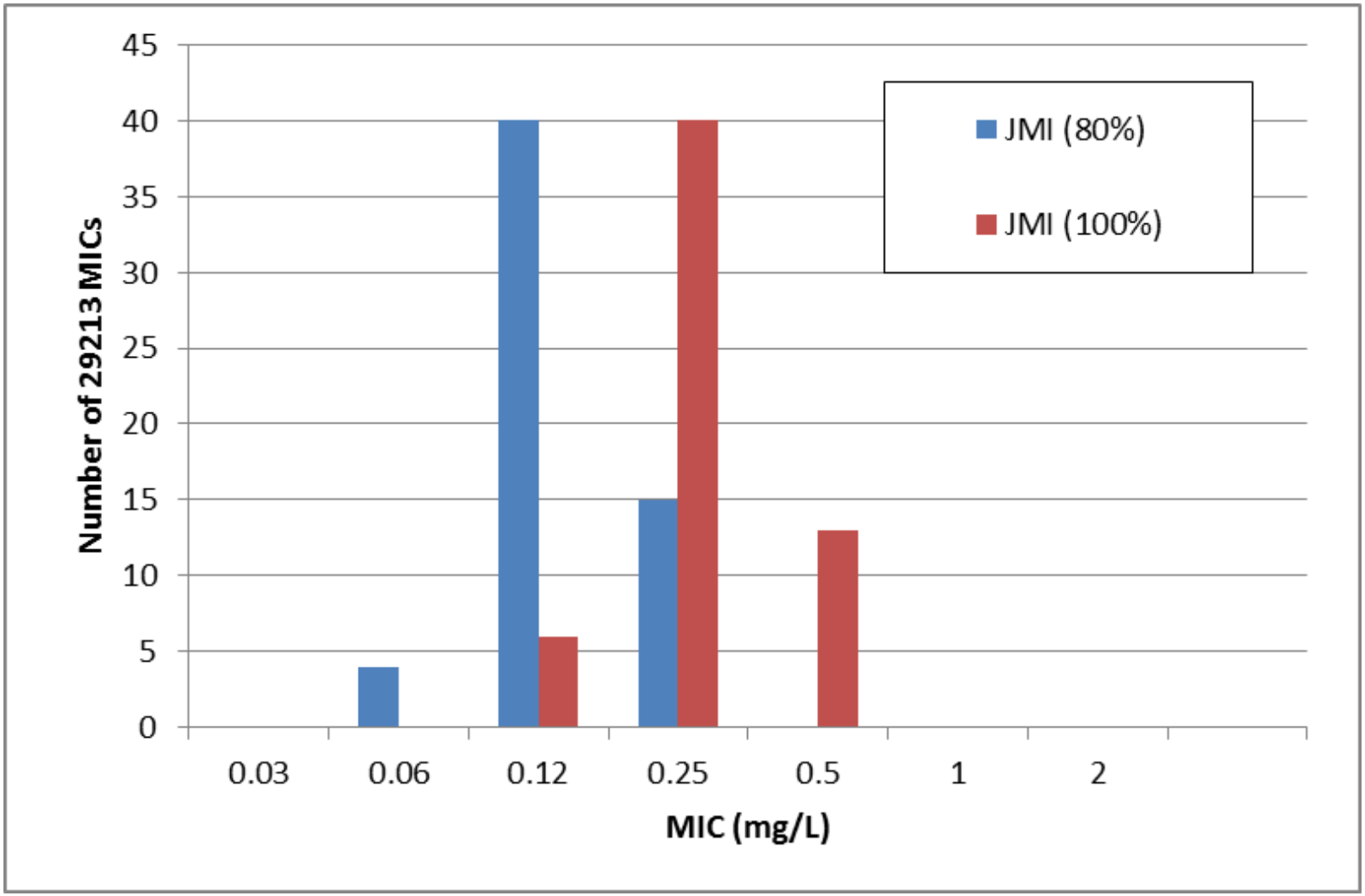
Subsequent Results Support Lower QC Range



IHMA Surveillance program QC data

Organism	N	No. occurrences at MIC (µg/mL)				
		0.06	0.12	0.25	0.5	1
S. aureus ATCC 29213	58			43	15	
E. faecalis ATCC 29212	51			45	6	
S. pneumoniae ATCC 49619	44	14	28	2		

Results From Alternative Approach Significantly Lower



Recommendations from WG

- Approved inclusion of verbiage as proposed by sponsor in M7-A11 (9/0/0)
- Recommended inclusion of a comment in next version of M100 explaining the trailing and how to read results in such cases (9/0/0)
- Sponsor agreed that a new QC study would be required to see whether multiple labs/readers can generate comparable results based on such instructions
  - Photos of findings would be taken for potential inclusion in subsequent version of M7

Shionogi

- Discuss methodologic path(s) forward for new drugs that aren’t compatible with current reference methods