

CLSI QCWG

2018 June

June 2018 QCWG

- Present: 10
 - **Sharon K. Cullen, B.S., RAC*, Maria M. Traczewski B.S. MT (ASCP)*, Michael D. Huband, B.S.**, Janet A. Hindler, MCLS, Patricia S. Conville, MS, MT (ASCP), Susan D. Munro, MT (ASCP), CLS, Mary K. York, PhD, ABMM, Chris Pillar, PhD, Dana Dressel, MT (ASCP), Elizabeth L. Palavecino M.D.,**
- Absent: 3
 - Dave Paisley, Erika Matuschek, Ph.D., Denise Holliday, MT (ASCP),

*co-chair, **recording secretary

June 2018 QCWG Agenda

- M23 Tier 2 Studies:
 - Cefpodoxime-ETX1317 (1:2) and Cefpodoxime MIC
 - Gepotidacin Disk
 - Imipenem-Relebactam and Imipenem Disk
 - Tebipenem Disk
- Troubleshooting guide (disk and MIC): Proposal to add β -lactam combination agents information
- Tier 3 QC: Review Tier 3 concerns and recommend additional actions
- M23 QC section: Initial discussion of potential changes

Drug: Cefpodoxime-ETX1317 (1:2)	Abbreviation: TBD	Previous ID: NA
Solvent: ??	Diluent: ??	Preparation: 1:2
Route of administration:	Class: β lactam combination	Subclass: NA
Study Report by: JMI	Pharma Co: Entasis Therapeutics	Control Drug: amoxicillin-clavulanate (2:1), piperacillin-tazobactam (fixed 4)

Footnotes:	<ul style="list-style-type: none"> Highlight on Table 5A-2, <i>K. pneumoniae</i> ATCC 700603 as QC strain for routine QC. <p>Follow up after QCWG (action item from meeting).</p> <ul style="list-style-type: none"> Cefpodoxime-ETX1317 (1:2) – “ETX1317 has demonstrated intrinsic activity against <i>E. coli</i>, therefore, <i>K. pneumoniae</i> ATCC 700603 should be used for routine QC testing of cefpodoxime-ETX1317 (1:2) as this strain can QC both components of the cefpodoxime-ETX1317 (1:2) combination.” <p>Follow up after QCWG:</p> <ul style="list-style-type: none"> Highlight on Table 5A-2, <i>E. coli</i> NCTC 13353 and <i>K. pneumoniae</i> ATCC 700603 for QC integrity check.
Discussion	<ul style="list-style-type: none"> Footnote needed to ensure <i>E. coli</i> NCTC 13353 is not used for routine QC since it appears from the MICs for the combination and single drug that this strain could also be a candidate for routine QC. Included strains with ranges in I-R category as QC integrity check. QCWG will review Table 4A-2 and 5A-2 in January 2019 to determine if footnotes or guidance should be added for others.

Drug Name:	Cefpodoxime-ETX1317 (1:2)	Votes:	9/0/0/1
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QC Strain	Range	% In	Mode	dil	Media	Labs	M23	Range Finder	Comments
<i>E. coli</i> 25922	0.03/0.06-0.12/0.25	100%	0.06/0.12	3	0.06/0.12	0.06/0.12	0.03/0.06-0.12/0.25, 100%, 3 dil	0.06/0.12-0.12-0.25, 100%, 2 dil	
<i>E. coli</i> 35218	0.03/0.06-0.12/0.25	100%	0.06/0.12	3	0.06/0.12	0.03/0.06 7 @ 0.06/0.12	0.03/0.06-0.12/0.25, 100%, 3 dil	Same	
<i>E. coli</i> NCTC 13353	0.06/0.12-0.25/0.5	100%	0.12/0.25	3	0.12/0.25	0.12/0.25	0.06/0.12-0.25/0.5, 100%, 3 dil	0.12/0.25-0.25/0.5, 100%, 2 dil	Add footnote to explain not to use for routine QC.
<i>K. pneumoniae</i> 700603	0.03/06-0.25/0.5	99.2%	0.12/0.25	4	2@0.06/0.12, 1@0.12/0.25	2@ 0.06/0.12 3 @ 0.06/0.12-0.12/0.25, 3@ 0.12/0.25,	0.03/06-0.25/0.5, 99.2%, 3 dil	Same	Shoulder 87% @ 0.06/0.12 Recommended routine QC strain

Drug Name:	Cefpodoxime	Votes:	9/0/0/1 *Items added after QCWG and not included in vote.
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QC Strain	Range	% In	Mode	dil	Shoulder	Media	Labs	M23	Range Finder	Comments
<i>E. coli</i> 25922	0.25-1	100%	0.5	3		0.5	0.5	0.25-1		Currently approved range
<i>E. coli</i> 35218	0.12-0.5	99.6%	0.25	3		0.25	0.25	0.12-0.5, 99.6%, 3 dil	0.12-0.5, 99.6%, 3 dil	
<i>E. coli</i> NCTC 13353	32-128	100%	64	3		64	64	32-128, 100%, 3 dil	64, 100%, 1 dil	100% of results at mode (64) Identify as QC integrity strain*
<i>K. pneumoniae</i> 700603	4-32	100%	16	4	79% @ 8	2@16, 1@8-16	3@8, 5@16	4-32, 100%, 3 dil	Same	Identify as QC integrity strain*

Drug: Gepotidacin	Abbreviation: GEP	Previous ID: GSK214944
Solvent: DMSO ^e	Diluent: Water	Preparation: 10 µg
Route of administration: PO/IV	Class: Triazaacenaphthylene	Subclass: NA
Study Report by: JMI	Pharma Co: GlaxoSmithKline	Control Drug: Ciprofloxacin

Footnotes:	None
Discussion	Table 6 and Glossary information previously added.

Drug Name:	Gepotidacin	Votes:	9/0/0/1
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QC Strain	Range	% In	Median	mm	Media	Disk	Labs	Gavan	Range Finder	Comments
<i>N.gonorrhoeae</i> 49226	32-40	98.5%	36	9	36	36	34, 35, 4@36, 37, 39	32-40, 98.5%, 9 mm	Same	Lab B mode outlier (39)

Drug: Imipenem-Relebactam	Abbreviation: IMR	Previous ID: ?
Solvent: relebactam: water	Diluent: relebactam: water	Preparation: 10/25µg disks
Route of administration: IV	Class: β lactam combination	Subclass: NA
Study Report by: IHMA	Pharma Co:	Control Drug: meropenem

Footnotes:	<ul style="list-style-type: none"> • Add to footnote: QC ranges for (add drug name here) were established using data from only one disk manufacturer. Disks from other manufacturers were not available at the time of testing. • Highlight on Table 4A-2, <i>K. pneumoniae</i> ATCC BAA-1705 and <i>K. pneumoniae</i> BAA-2814 as QC strain for routine QC for imipenem-relebactam. • Highlight on Table 4A-2, <i>K. pneumoniae</i> ATCC BAA-1705 for QC integrity check for imipenem. ??? • Add to Table 4D Troubleshooting Guide (Cefepime and <i>A. baumannii</i> NCTC 13304 regarding “read inner zone...when discreet colonies within zone are seen” , imipenem, <i>K. pneumoniae</i> ATCC BAA-1705 and <i>K. pneumoniae</i> BAA-2814
Discussion	<ul style="list-style-type: none"> • Objective of study was to add QC strains for IMR and Imipenem alone • Table 6 and Glossary information previously added. • Note: Abbreviation needs to be added to M100 29th Edition in Glossary II. • Routine QC strains are same as those identified for MIC on Table 5A-2. • QC integrity check: not needed for <i>K. pneumoniae</i> BAA-2814, <i>K. pneumoniae</i> ATCC BAA-1705 has a broad (12 mm) QC range, meropenem can be used so strains recommended for imipenem. • Need to add address reading when breakthrough colonies that are seen with single drug during QC integrity check.

Drug Name:	Imipenem-Relebactam	Votes:	7/2/0/1 (ranges), 9/0/0/1 (routine QC strains)							
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QC Strain	Range	% In	Median	mm	Media	Disk	Labs	Gavan	Range Finder	Comments
<i>E. coli</i> 25922	27-33	99.4%	30	7	30	30	4@30, 5@31	27-33, 99.4%, 7 mm	28-33, 98.7%, 6 mm	Lab 7 mode outlier
<i>P. aeruginosa</i> 27853	26-31	100%	29	6	29	29	3@28, 4@29, 2@30	27-33, 98.7%, 7 mm	26-31, 100%, 6 mm	
<i>K. pneumoniae</i> 700603	26-32	100%	29	7	29	29	6@29, 3@30	26-32, 100%, 7 mm	Same	
<i>K. pneumoniae</i> BAA-1705	23-29	98.5%	26	7	26	26	2@25, 4@26, 3@27	23-29, 98.5%, 7 mm	Same	Routine QC strain
<i>K. pneumoniae</i> BAA-2814	21-28 22-28	99.6% 96.5%	25	8 7	2@24, 1@25	25	5@24, 2@25, 2@26	21-28, 99.6%, 8 mm	Same	Lab 3 mode outlier. Approved smaller range for better control. Routine QC strain

Drug Name:	Imipenem	Votes:	7/1/0/1 (ranges) Need footnote to read inner colonies for zone diameter. 10/0/0/0 (change cefepime description of QC ranges to be consistent) <i>E. coli</i> ATCC 13353 from ≤15 to 6-15 mm <i>A. baumannii</i> NCTC 13304 from ≤16 to 6-16 mm
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QC Strain	Range	% In	Median	mm	Media	Disk	Labs	Gavan	Range Finder	Comments
<i>K. pneumoniae</i> BAA-1705	11-22	98.1%	16	12	16	15, 17	2@14, 2@15, 1@16, 3@17, 1@20	12-20, 92.4%, 9 mm	11-22, 98.1%, 12 mm	
<i>K. pneumoniae</i> BAA-2814	6-14	95.7%	10	9	1@8, 2@10	1@9, 1@11	6, 7, 8, 9, 10, 11, 2@12, 14	6-14, 95.7%, 9 mm	4-16, 99.6%, 13 mm	

Drug: Tebipenem	Abbreviation: TBP	Previous ID: SPR859
Solvent: Water	Diluent: Water	Preparation: 10 µg disk
Route of administration: PO	Class: Carbapenem	Subclass: Carbapenem
Study Report bty: IHMA	Pharma Co: Spero Therapeutics	Control Drug: Imipenem, Meropenem

Footnotes:	Add to Table 4A-1, QC range for <i>K. pneumoniae</i> ATCC 700603 with tebipenem is 26-32 and is considered a supplemental QC strain and is not required for routine QC of tebipenem MIC tests.
Discussion	PO administration as SPR994, pa pivoxil prodrug of SPR859 Ranges were established for <i>K. pneumoniae</i> ATCC 700603 as supplemental for use in various studies since the drug is targeting ESβLs but not needed for routine QC.

Drug Name:	Tebipenem	Votes:	8/0/0/1 for <i>E. coli</i> ATCC 25922 8/0/0/1 Changed range for <i>P. aeruginosa</i> ATCC 27853 to 7 mm 8/0/0/1 <i>K. pneumoniae</i> ATCC 700603 8/0/0/1 <i>S. aureus</i> ATCC 25923 no range approved
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QC Strain	Range	% In	Median	mm	Media	Disk	Labs	Gavan	Range Finder	Comments
<i>E. coli</i> 25922	30-37	99.3%	33	8	3@32, 2@33, 2@34, 2@36	33	2@33, 34	30-36, 94.1%, 7 mm	30-37, 99.3%, 8 mm	Selected 8 mm ranges to achieve >95% in range.
<i>P. aeruginosa</i> 27853	19-27 20-26	99.4% 96.5	23	9 7	2@24, 23	23	2@22, 3@23, 3@24, 26	20-26, 96.5%, 7 mm	19-27, 99.4%, 9 mm	Lab 5 mode outlier-26 7mm range preferred
<i>K. pneumoniae</i> 700603	26-32	99.2%	29	7	28, 2@29	29	3@28, 2@29, 3@30	26-32, 99.2%, 7 mm	Same	Lab 4 mean and mode outlier – data eliminated. Supplemental QC
<i>S. aureus</i> 25923	34-45 No range	97.6%	40	12	40, 2@41	40, 41	35, 2@37, 40, 2@41, 2@43, 44	35-45, 93.5%, 11 mm	33-47, 100%, 15 mm	Lab 2 1, 2, 5 mode outliers Large lab variability

Tier 3 MIC – Data Requested

QC Strain (ATCC)	Antimicrobial	Current Range	Action Recmd	Concern	Date Reported
<i>S. pneumoniae</i> ATCC 49619	Levofloxacin	0.5-2	Request data/feedback	Modal 0.5 µg/mL among 1,520 values for 88.5% of results. Consider revising to 0.25-1. (Table 3-27). Refer to USCAST Quinolone report V1.2.	Jan-18
<i>S. aureus</i> ATCC 29213	Ciprofloxacin	0.12-0.5	Request data/feedback	"bi-modal" MIC distribution noted from three studies. Consider revising range to 0.12-1. (Table 3-28). Refer to USCAST Quinolone report V1.2.	Jan-18
<i>H. influenzae</i> ATCC 49247	Moxifloxacin	0.008-0.03	Request data/feedback	80.0% at upper extreme (0.03 µg/mL) of MIC range (results from only one study, Table 3-29) Refer to USCAST Quinolone report V1.2.	Jan-18
<i>E. faecalis</i> 51299	Gentamicin HLAR	Resistant	Request data/feedback	Out of range results (susceptible). Organism stability.	Jun-2017
<i>S. pneumoniae</i> ATCC 49619	Cefuroxime	0.25-1	Request data/feedback	Mode at 0.25	Jun-2013

Tier 3 MIC – Remove 2013-2015 Reports Unless Feedback Received

QC Strain (ATCC)	Antimicrobial	Current Range	Action Recmd	Concern	Date Reported
K. pneumoniae 700603	Imipenem/relebactam	0.03-0.25	Monitor/request feedback	>5% out high reported with one lab	Jan-18
K. pneumoniae BAA-2814	Imipenem/relebactam	0.06-0.25	Monitor/request feedback	>5% out high reported with one lab. (BAA-2814 or BAA-1705 used for routine QC)	Jan-18
E. faecalis 29212	Amikacin	64-256	Monitor/request feedback	CDC reported out low when testing gram neg panels, other strains in range.	Jan-18
E. coli NCTC 13486	Colistin	NA	Potential QC organism	MICs in range likely tested (e.g., MIC = 4 µg/ml) Potentially more reproducible than current QC	Jan-2017
E. faecalis 29212	Gentamicin	4-16	Monitor/request feedback	Some out low. Cations, pH in range	Jan-2015
E. faecalis 29212	Tobramycin	8-32	Monitor/request feedback	Some out low. Cations, pH in range	Jan-2015
P. aerug 27853	Etrapanem	2-8	Monitor	Out low with some labs	NA
E. faecalis 29212	Minocycline	1-4	Monitor/request feedback	Mode at low end at 16 hrs, bimodal at 18 hrs, at middle of range at 20 hrs	NA
S. aureus 29213	Minocycline	0.06-0.5	Monitor/request feedback	Mode at low end of current range regardless of read time 16-20 hr	Jun-2013
B. fragilis 25285	Pip/tazo	0.12-1	Monitor/request feedback	Out low (control M23 study Jan 2010)	Jun-2013

Tier 3 Disk Diffusion – Additional Data or Analysis For Jan 2019 Meeting

QC Strain (ATCC)	Antimicrobial	Current Range	Action Recmd	Concern	Date Reported
<i>P. aeruginosa</i> 27853	Imipenem	20-28	Consider tightening range to 20-26 (98% in range), or 20-27 (99% in range). Analyze by gavan and rangefinder	Zones in the lower part or below range reported (1600 results, including 480 from 2001 M23)	Dec-15
<i>E. coli</i> 25922	Pefloxacin	25-33	EUCAST range 26-32 (07% in range). CLSI 25-33 (100% in range). Clearer reading instructions (inner or outer zone diameters, pictures) and/or address in troubleshooting guide.	Is there a better way to QC this agent? Varies by manufacturer.	Jan-17
<i>P. aeruginosa</i> ATCC 27853	Ceftriaxone	17-23	Request data, reassess range or troubleshooting information.	Colonies within zone causing, out of range	Jun-17
<i>P. aeruginosa</i> ATCC 27853	Amikacin	18-26	Suggest changing to 20-26. Aligns with changes to Gentamicin and Tobramycin. Is data from original M23 available? Analyze by gavan and rangefinder	Out high for many labs, 781 results. No results at 18-19	Jan-18

Tier 3 Disk Diffusion – Miscellaneous Requests

QC Strain (ATCC)	Antimicrobial	Current Range	Action Recmd	Concern	Date Reported
<i>K. pneumoniae</i> 700603	β lactam/ β lactamase inhibitors	No range	Request ranges for single and combination agents, e.g., amoxicillin, ampicillin, ampicillin-sulbactam (2:1), cefepime, ceftaroline	Alternative for E. coli 35218	NA
<i>S. aureus</i> 25923	Tedizolid	NA	Request Tier 2 study to establish QC ranges. (Methods Working Group).	Need new Tier 2 study for QC range if disk mass is changed from 20 to 2 μ g	Jan-17
<i>S. aureus</i> 25923	Linezolid	NA	Request Tier 2 study to establish QC ranges. (Methods Working Group).	Need new Tier 2 study for QC range if disk mass is changed from 30 to 10 μ g.	Jan-17

Table 5G: Troubleshooting Guide - 9/0/0/0

Make similar changes to Disk Troubleshooting

General Comment

- (1) QC organism maintenance: Avoid repeated subcultures. Retrieve new QC strain from stock (refer to M07,¹ Subchapter 4.4). If using lyophilized strains, follow the maintenance recommendations of the manufacturer. ~~Store *E. coli* ATCC^{®*} 35218, and *K. pneumoniae* ATCC[®] 700603 stock cultures at -60°C or below and prepare working cultures weekly~~

Table 5G: Troubleshooting Guide – Deleted Text

Antimicrobials Agent	QC Strain	Observation	Probable Cause	Comments/Suggested Actions
β-LACTAMS				
Amoxicillin-clavulanate Ticarcillin-clavulanate	<i>E. coli</i> ATCC® 35218 <i>K. pneumoniae</i> ATCC® 700603	MIC too high	Clavulanate is labile. Antimicrobial agent is degrading.	Use alternative lot. Check storage conditions and package integrity.
Aztreonam Cefotaxime Cefpodoxime Ceftazidime Ceftriaxone	<i>K. pneumoniae</i> ATCC® 700603	MIC too low	Spontaneous loss of the plasmid encoding the β-lactamase	See general comment (1) on QC organism maintenance.

Table 5G: Troubleshooting Guide – Revised Text

Antimicrobial Agent	QC Strain	Observation	Probable Cause	Comments/Suggested Actions
β-LACTAMS				
Combination β-Lactam agents	<i>A. baumannii</i> ATCC 13304 <i>E. coli</i> ATCC 35218, <i>E. coli</i> ATCC 13353, <i>K. pneumoniae</i> ATCC 700603, <i>K. pneumoniae</i> ATCC BAA-1705,	MIC too low or susceptible for single β-lactam agent, in range for combination β-lactam agent	Spontaneous loss of the plasmid encoding the beta-lactamase	Obtain new frozen or lyophilized stock culture. Use other routine QC strain (if available). These strains should be stored at -60C or below and avoid frequent subcultures. Note: <i>K. pneumoniae</i> BAA-2814 is stable and doesn't require QC integrity check.
Combination β-Lactam agents	<i>A. baumannii</i> ATCC 13304 <i>E. coli</i> ATCC 35218, <i>E. coli</i> ATCC 13353, <i>K. pneumoniae</i> ATCC 700603, <i>K. pneumoniae</i> ATCC BAA-1705, <i>K. pneumoniae</i> ATCC BAA-2814	MIC too high or resistant for both the single β-lactam agent and the combination β-lactam agent	Antimicrobial agent is degrading	Use alternative lot of test materials. Check storage and package integrity. Imipenem and clavulanate are especially labile.

Proposed Q&A – Concept Supported But No Vote

Question: Can you provide guidance on the QC strains to test routinely for new β -lactam combination agents? Can we continue to use *E. coli* ATCC 25922, *E. coli* ATCC 35218 and *P. aeruginosa* ATCC 27853 which have traditionally been our routine QC?

Answer

Routine QC strains for β -lactam combination agents are identified in Table 4A-2 and 5A-2. Different QC strains are required for various agents based on the activity of the antimicrobial agent and the characteristics of the QC strain. Use of other strains may not adequately assess the quality of the test materials.

Refer to The CLSI AST News Update Volume 3, Issue 2 Spring 2018,
Featured Article: Part 2 Why all the fuss over quality control of β -lactam combination agents?

While QC recommendations are often also applicable also to commercial AST methods, when using a commercial AST device, you should follow QC recommendations in the manufacturer's instructions for use.