

CLSI Minutes of the Quality Control Working Group

Ft. Lauderdale, FA January, 2015

Present: Steve Brown, Sharon Cullen, Susan Munro, Bob Rennie, Ross Mulder, Mary York, Michael Huband
Dwight Hardy, Patricia Conville, Robert Flamm, Janet Hindler, Stephen Hawser

Quality Control Ranges Approved by the QC Working Group

Name	AZD0914	Previous ID		Abbrev	TBD	Study coordinator: CMI, Pharma sponsor: Aztra Zeneca	Votes (For/Opposed/ Abstained/ Not present)
Solvent	DMSO	Diluent	DMSO	Rev History			
Route of Administration		Class	Spiropyrimidine trione (a DNA Gyrase inhibitor distinct from quinolones)	Subclass	TBD		
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	MODE	Shoulder %	Variability/Comments	
S. aureus ATCC 29213		0.12-05	100.0%	0.25		media variability	9/0/1/1
E. faecalis ATCC 29212		0.25-2	100.0%	0.5	93.3% @ 1	media and lab variability. Rangefinder recommended 3 dil range	9/0/1/1
E. coli ATCC 25922		1-4	100.0%	2			9/0/1/1
S. pneumoniae ATCC 49619		0.12-0.5	100.0%	0.25			9/0/1/1
H. influenzae ATCC 49247		0.12-1	100.0%	0.5	82.7% @ 0.25	Rangefinder recommended 3 dil range	9/0/1/1

Name	Delafloxacin	Previous ID		Abbrev	DLX	Note: Confirm glossary info used is from Chris's presentation	
Solvent	1/2 volume of water, then 0.1 mol/L NaOH driewise to dissolve	Diluent	Water	Rev History		Presented by MicroMx,	
Route	IV/PO	Class	Quinolone	Subclass	Fluoroquinolone		
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	MODE	Shoulder %	Variability/Comments	Votes (For/Opposed/ Abstained/ Not present)
E. coli ATCC 25922		28-35	100.0%	31		Rangefinder range proposed Gavin proposed was 97% in range.	12/0/0/0 (vote #1)
P. aeruginosa ATCC 27853		23-29	99.2%	25 & 26		Rangefinder & Gavan agree	12/0/0/0 (vote #1)
S. aureus ATCC 25923		32-40	98.8%	35 & 36		Rangefinder & Gavan agree. 60 results from lab 1 were removed as outliers and 6 results from lab 8 were removed (out of QC for control). Add statement to troubleshooting guide about zones too large, refer to reading instructions for fuzzy zones.	12/0/0/0 (vote #1)
S. pneumoniae ATCC 49619		29-36	99.7%	32		Rangefinder. 60 results from lab 1 were removed as outliers and 60 results from lab 8 were removed (out of QC for control). Only have 6 labs (M23 requires 6). Both labs read larger. Could age of inoc also contribute? Recommend investigate and new study	12/0/0/0 (vote #2) to reject
H. influenzae ATCC 49247		40-51 40-52	97% 99.2%	45		Note: Largest range for H. influ is 12 mm for clinafloxacin. Combination of range finder and Gavin to get >95% in range using 12 mm zone size	12/0/0/0 (vote #3)

S. aureus ATCC 29213		0.001-0.008	99.2%	0.002	86.0% @ 0.004	Some lot-to-lot variability with Lot A giving primarily lower MICs and lot C giving higher MICs	12/0/0/0 (vote #4)
E. faecalis ATCC 29212		0.015-0.12	100.0%	0.06	92.5% @ 0.03		12/0/0/0 (vote #4)
S. pneumoniae ATCC 49619		0.004-0.015	98.9%	0.008			12/0/0/0 (vote #4)
E. coli ATCC 25922		0.008-0.03	96.3%	0.015	52.70%	Rangefinder suggested 0.004 - 0.03	12/0/0/0 (vote #4)
P. aeruginosa ATCC 27853		0.12-0.5	99.6%	0.25			12/0/0/0 (vote #4)
H. influenzae ATCC 49247		≤0.002 0.00025-0.001	100.0%	0.0005		Some off scale but number of results at ≤0.0025 are so few (11) that it wouldn't change the recommendation. In the future, do we need another QC strain that will be on scale with dilutions likely to be tested?	12/0/0/0 (vote #5)

Name	Solithromycin	Previous ID	CEM101	Abbrev	SOL		
Solvent	0.05% glacial acetic acid/	Diluent	water	Rev History			
Route of Administration		Class	fluoroketolide	Subclass		Presented by JMI, Pharma sponsor Cembra	
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	MODE	Shoulder %	Variability/Comments	Votes (For/Opposed/ Abstained/ Not present)
N. gonorrhoeae ATCC 49226		34-42 mm 33-43 mm	95.8% 98.5%	38 mm		Rangefinder 33-43 mm, some disk lot variability, also see result of 43 in media lots	10/0/2/0
N. gonorrhoeae ATCC 49226		0.03-0.25	100.0%	0.12	80.5% @ 0.06	By agar dilution, lab variabilty	10/0/2/0

Name	S-649266	Previous ID		Abbrev			
Solvent	0.85% SALINE	Diluent	0.85% SALINE	Rev History			
Route of Administration		Class	β-lactam	Subclass	Siderophore cephalosporin	<p>To correlate in vitro and in vivo results, need to reduce iron (esp with ITT Acinetobacter spp.). Will pursue modification of reference method for future to address this issue and conduct M23 study to propose QC for modified method (ideally without use of proprietary materials e.g. modification for CAMHB to reduce iron vs use of Iso sensitest and chelex). Proposal for CAMB is an interim proposal.</p> <p>Note: Trailing is observed when reading MIC - suggest further assessment and potential guidance on reading or confirm if instructions for reading sulfonamides could be used. Use of new materials would need to include studies of multiple lots/mfg. Recommendations should go to methods WG first and then do M23 Tier 2 study</p>	
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	MODE	Shoulder %	Variability/Comments	Votes (For/Opposed/ Abstained/ Not present)
E. coli ATCC 25922		0.06-0.5	100.0%	0.25			11/0/1/0
P. aeruginosa ATCC 27853		0.5-4	97.5%	0.5	61.2% @ 1		11/0/1/0

Name	Amikacin/ Fosfomycin (5/2)	Previous ID		Abbrev		Presented by JMI	
Solvent	Amikacin - Water, Fosfomycin--Water	Diluent	Amikacin - Water, Fosfomycin--Water	Rev History			
Route of Administration		Class	Aminoglycoside/ fosfomycin combination drug	Subclass		Method: Includes Glucose 6 Phosphate. Concentration listed represents level of amikacin. Do we need to address sections in text with dosage (since it is an infusion). Request QC strains that confirm both adequate amounts of both drugs (e.g., like E. coli 35218). JMI has been running single drugs from same lot concurrently. Note: fosfomycin alone is currently approved only for agar due to skipped wells in broth. This wasn't observed in this combination and agar and broth data meets acceptance criteria.	
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	MODE	Shoulder %	Variability/Comments	Votes (For/Opposed/ Abstained/ Not present)
S. aureus ATCC 29213 by broth		0.5-4	100.0%	2	85.8% @ /1	Broth range approved also addresses agar dilution data	8/2/1/1
E. faecalis ATCC 29212		32-128	100.0%	64			8/2/1/1
E. coli ATCC 25922		0.5-2 0.25-2	100.0%	1		Range expanded to 4 dilution to address both broth and agar data	8/2/1/1
P. aeruginosa ATCC 27853 by broth		2-8 1-8	99.7%	4	shoulder 49% at 2	Range expanded to 4 dilution to address both broth and agar data	8/2/1/1
H. influenzae ATCC 49247		0.5-4	97.8%	1	64.3 @ /2		8/2/1/1

S. pneumoniae ATCC 49619		8-64	100.0%	32	69.2% @ 16		8/2/1/1
S. aureus ATCC 29213 by Agar Dilution		0.5-2	100.0%	1			broth range also addresses agar
E. coli ATCC 25922 by Agar Dilution		0.25-2	100.0%	1	64.4% @ 0.5		broth range also addresses agar
P. aeruginosa ATCC 27853 by Agar Dilution		1-8	100.0%	2	69.5% @ 4		broth range also addresses agar

Name	Azithromycin	Previous ID		Abbrev			
Solvent	95% ethanol or glacial acetic acid	Diluent	Broth Media	Rev History			
Route of Administration		Class	Macrolide	Subclass			
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	MODE	Shoulder %	Variability/Comments	Votes (For/Opposed/ Abstained/ Not present)
N. gonorrhoeae ATCC 49226		0.25-1	97.6%	0.5		by agar dilution, some media variability	11/0/0/1

Name	Cefepime/ Tazobactam @ fixed 8 µg/ml	Previous ID	WCK 4282	Abbrev		Presented by JMI, Pharma sponsor Wockhardt	
Solvent	Cefepime - Phosphate buffer. Tazobactam-water	Diluent	Cefepime - Phosphate buffer. Tazobactam-water	Rev History			
Route of Administration		Class	B-lactam/β- lactamase inhibitor combination	Subclass			
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	MODE	Shoulder %	Variability/Comments	Votes (For/Opposed/ Abstained/ Not present)
S. aureus ATCC 29213		1-4	100.0%	2			10//0/1/1 (vote #1)
E. coli ATCC 25922		0.03-0.12	100.0%	0.06			10//0/1/1 (vote #1)
K. pneumoniae ATCC 700603		0.12-0.5	99.2%	0.25		Strain is not best to determine TAZ activity. Cefepime alone = 0.5-1	10//0/1/1 (vote #1) Include ranges for Cefepime alone.
E. coli NCTC 13353		0.12-0.5 0.06-0.5	95.8% 100%	0.25	47% @ .5	Rangefinder 0.06-0.5. Better indicator of TAZ activity. Cefepime alone = >4	10//0/1/1 (vote #1) Include ranges for Cefepime alone.
P. aeruginosa ATCC 27853		0.5-4	100.0%	1	87.8% @ 2	Per Jim Ross: ATCC can get org from NCTC. Request will be made to ATCC to be available prior to market release	10//0/1/1 (vote # 2)
H. influenzae ATCC 49247		0.5-2	100.0%	1			10//0/1/1 (vote # 2)

S. pneumoniae ATCC 49619		0.03-0.12	100.0%	0.06			10//0/1/1 (vote # 2)

Name	Meropenem/ RPX7009 @ fixed 8 µg/ml	Previous ID		Abbrev		Presented by JMI, Pharma sponsor Rempex (The Medicines Company)	
Solvent	9/10 DMSO	Diluent	Water	Rev History			
Route of Administration		Class	B-lactam/β- lactamase inhibitor combination	Subclass		Follow up question: Which is better QC for combo? Need for tables or potentially for troubleshooting	
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	MODE	Shoulder %	Variability/Comments	Votes (For/Opposed/ Abstained/ Not present)
S. aureus ATCC 29213		0.03-0.12	100.0%	0.06			10/0/1/1
E. coli ATCC 25922		0.008-0.06	100.0%	0.03	72.0% @ 0.015		10/0/1/1
E. coli ATCC 35218		0.008-0.06 0.015-0.06	100% 98.3	0.03	60.0% @ 0.015	Range Finder 0.015 – 0.06. Some lab and media variability. Request fluture proposal for Meropenem alone (data is available for one lot but was not included in Agenda)	10/0/1/1
P. aeruginosa ATCC 27853		0.12-1	100.0%	0.03	65.3% @ 0.5		10/0/1/1
K. pneumoniae ATCC 700603		0.015-0.06	99.6%	0.03			10/0/1/1
K. pneumoniae ATCC BAA1705		0.015-0.06	97.1%	0.25			10/0/1/1

Name	Meropenem/ RPX7009 @ fixed 4 µg/ml	Previous ID		Abbrev		Request has been withdrawn by sponsor	
Solvent	9/10 DMSO	Diluent	Water	Rev History			
Route of Administration		Class	B-lactam/β- lactamase inhibitor combination	Subclass			
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	MODE	Shoulder %	Variability/Comments	Votes (For/Opposed/ Abstained/ Not present)
S. aureus ATCC 29213		0.03-0.12	100.0%	0.06		Request has been withdrawn by sponsor	
E. coli ATCC 25922		0.015-0.06	100.0%	0.03		Request has been withdrawn by sponsor	
E. coli ATCC 35218		0.015-0.06	100.0%	0.03		Request has been withdrawn by sponsor	
P. aeruginosa ATCC 27853		0.12-0.5 0.12-1	92.3% 100%	0.03		Request has been withdrawn by sponsor	
K. pneumoniae ATCC 700603		0.015-0.06	98.6%	0.03		Request has been withdrawn by sponsor	
K. pneumoniae ATCC BAA1705		0.015-0.06	99.5%	0.25		Request has been withdrawn by sponsor	

Name	Eravacycline	Previous ID		Abbrev		Presented by IHMA,	
Solvent		Diluent		Rev History			
		Class	Tetracycline	Subclass			
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	MODE	Shoulder %	Variability/Comments	Votes (For/Opposed/ Abstained/ Not present)
C. difficile ATCC 700057		0.06-0.25	99.6%	0.12			10/0/1/1
B. fragilis ATCC 25285		0.06-0.25	100.0%	0.12			10/0/1/1
B. thetaiotaomicron ATCC 29741		0.12-1	100.0%	0.25	93.6% @ 0.5	lab variability	10/0/1/1
E. lentum ATCC 43055		No Range. Results off-scale @ ≤0.03					10/0/1/1

Name	Meropenem						
S. pneumoniae ATCC 49619		0.03-0.25	100.0%	0.06	79% @ 0.12	Original Tier 2 - using today's criteria would establish 4 dilution range. Additonal Tier 3 data also supports expansion of range to 4 dilutions.	10/1/0/1

IQCP

Ad hoc Sub-Working Group chaired by Susan Munto. Supportive information presented by Luann Ochs.

The group discussed the processes that laboratories can use to develop their own QC plan, as noted in the CMS announcement, S&C: 15-07-CLIA, Effect on Microbiology Laboratories Due to the Removal of References to the Clinical Laboratory and Standards Institute (CLSI) and to CLSI Documents, issued on October 31, 2014

As of January 2016, US labs will need to create an Individual QC Plan unless they do QC each day of test per CLIA regulations since the "equivalent" QC plan will be eliminated as an option in the CLIA regulations. As of January 2016, the IQCP (per CLSI EP-23) will be the only acceptable approach to streamline/modify traditional QC requirements in CLSI regulations. This Ad Hoc working group is working on templates that labs can use to create their IQCP for AST. CLSI QC Working Group can enhance some of our activities to support this better (e.g., expand troubleshooting information, identify sources of errors for AST as we review QC and breakpoints for new drugs.

This means each lab will need to create IQCP for each test they don't want to do daily positive and negative QC testing (all areas of labs except for anatomical pathology). This involves doing risk analysis to determine what can go wrong and determine what is done to address any risks that are unacceptable. You likely do everything you need to do already, this will require you to go through the assessment and document it. It could lead to adding new procedures or doing additional QC (if you find something that isn't sufficiently mitigated). It also could be used to justify further streamlining of your QC.

Respectfully submitted,

Steven Brown

**Co-Chair, Quality Control Working
Group**

January 2015, Ft. Lauderdale, FA

**Do we add comment about
testing with and without
TAZ? Do we also need to
approve Cefepime only
range for any bugs?**