CLSI QCWG

June 2013

QCWG Members

Sharon Cullen (co-chair)	Siemens (MicroScan)	Dx Industry
Steven Brown, Ph.D (co-chair)	CMI	QC/Research Studies
Bill Brasso	Becton Dickinson	Dx Industry
Bob Rennie, Ph.D.	U. of Alberta	Clinical Lab/Broth QC
Janet Hindler	UCLA	Clinical Lab
Susan Munro	Palo Alto, CA	Clinical Lab
Ron Jones, M.D.	JMI	QC/Research Studies
Michael Huband*	Pfizer	Pharmaceutical Industry
Frank Wegerhoff	Covance Central Lab Services	Clinical Research Organiza
Erika Matuschek*	EUCAST	Clinical Lab
Ross Mulder	bioMerieux-Vitek	Dx Industry
Stephen Hawser*	IHMA	Clinical Lab & Industry Su
Patricia (Patti) Conville	FDA (OIVD)	Government

*Not present

New members

CLSI QCWG Agenda

- M23 Tier 2 Studies – None submitted for this meeting!
- User QC questions and revisions (Susan Munro and Ad Hoc User QC)
- Data Collection Plan to potentially support reduced QC when adding a new antimicrobial agent to an existing system (Chris Doern)
- Actions for 2014 meetings –
  - Recommendations for testing β lactam and carbapenem inhibitor combinations
  - Comprehensive review/clean up of QC tables/text
  - Tier 3 QC: request for data, actions for 2014

User QC Ad Hoc Working Group

Susan Munro, leader

Denise Holliday, recording secretary

Members: Janet Hindler, Susan Sharp, Nancy Watz, Mary York

Agenda Book References

3 1_Non fermenter Routine QC.pdf

3 2_Q A conversion to weekly QC.pdf

3 3_One QC result out use results prev lot.pdf

User QC Agenda item 1

<u>Request for vote</u>: WG Approved 6/0/5 (For/opposed/absent).

Topic: To clarify recommendations for routine QC for Enterobacteriacea and non-fermenting gram negative rods in Tables 2A, 2B-1 to 2B-5, M100-S24.

Background:
Questions from users have been received by members of the group regarding the necessity to test multiple QC strains when performing daily QC (includes "with each use") or weekly QC. If 2 or more QC strains have QC ranges in QC Tables 3 and 4 do all have to be tested? Also when a physician requests a single drug for additional susceptibility testing, is more than one QC strain necessary?

User QC Agenda item 1

Proposal

- **Identify *E. coli* ATCC® 25922 for *Enterobacteriaceae and Pseudomonas aeruginosa ATCC®* 27853 for non-fermenters as the routine QC strain for most antimicrobial agents.**
- **List the exceptions where a different QC strain should be tested**

Rationale:

- **Prefer to test QC strains with similar growth requirements for the clinical isolates tested (e.g. *E. coli ATCC® for Enterobacteriaceae and Pseudomonas aeruginosa* ATCC® 27853 for non-fermenters).**
- **If this QC strain has no QC range for an antimicrobial agent or does not provide optimum QC for the antimicrobial agent (e.g. MIC QC range very high or very low), recommend other QC strains for that antimicrobial agent.**
- **Minimize need for multiple QC strains when testing single agents**
- **Note: no change in recommendation to use *Escherichia coli* ATCC® 35218 for inhibitor combination agents.**

Future Plans:

- **Add guidelines when to test routinely in M2/M7/M100**

Current M100-S23 with revisions approved at Jan 2013 meeting 2A for *Enterobacteriaceae*

Routine Quality Control (QC) Recommendations (See Tables 3A and 4A for acceptable QC ranges.)

***Escherichia coli* ATCC®* 25922**
***Pseudomonas aeruginosa* ATCC® 27853 (for carbapenems)**
***Escherichia coli* ATCC 35218 (for β-lactam/β-lactamase inhibitor combinations)**

Current M100-S23 with revisions approved Jan 2013
2B-1 for *Pseudomonas aeruginosa*

Routine QC Recommendations (See Tables 3A and 4A for acceptable QC ranges.)

***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

NOTE: DELETED FROM BOX: *Escherichia coli* ATCC® 25922

Current M100-S23 (2B-2, 2B-3, 2B-4, 2B-5 for other nonfermenters)

Routine QC Recommendations (See Tables 3A and 4A for acceptable QC ranges.)

***Escherichia coli* ATCC® 25922**
***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

Proposed M100-S23: Revisions approved at Jan 2013 meeting 2A for *Enterobacteriaceae*

Routine Quality Control (QC) Recommendations (See Tables 3A and 4A for acceptable QC ranges.)

***Escherichia coli* ATCC®* 25922**
***Pseudomonas aeruginosa* ATCC® 27853 (for carbapenems)**
***Escherichia coli* ATCC 35218 (for β-lactam/β-lactamase inhibitor combinations)**

Proposed M100-S23 with revisions approved Jan 2013
2B-1 for *Pseudomonas aeruginosa*

Routine QC Recommendations (See Tables 3A and 4A for acceptable QC ranges.)

***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

NOTE: DELETED FROM BOX: *Escherichia coli* ATCC® 25922

Proposed:

Acinetobacter spp. Table 2B-2

Routine QC Recommendations (See Tables 3A and 4A for acceptable QC ranges.)

***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 25922 (for tetracyclines and trimethoprim-sulfamethoxazole)**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

Proposed:

Burkholderia cepacia Table 2B-3

Routine QC Recommendations (See Tables 3A and 4A for acceptable QC ranges.)

***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 25922 (for chloramphenicol, minocycline, and trimethoprim-sulfamethoxazole)**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

Proposed:

Stenotrophomonas Table 2B-4

Routine QC Recommendations (See Tables 3A and 4A for acceptable QC ranges.)

***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 25922 (for chloramphenicol, minocycline, and trimethoprim-sulfamethoxazole)**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

Proposed:

Other non-Enterobacteriaceae Table 2B-5

Routine QC Recommendations (See Table 4A for acceptable QC ranges.)

***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 25922 (for chloramphenicol, tetracyclines, sulfonamide, and trimethoprim-sulfamethoxazole)**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

User QC Ad Hoc WG: Agenda item 2

Request for vote: WG Approved 6/0/5 (For/opposed/absent).

Topic:
•Using retrospective QC data to convert from daily (with each use) to weekly QC testing.
•Question submitted from user and publish as Q & A

Question:
"Previously, Antibiotic A was not on our routine test panel. When we were asked to test Antibiotic A on a patient's isolate, we tested the patient's isolate and performed QC testing for Antibiotic A on the same day. Now we want to begin testing Antibiotic A routinely. Can we use the last 20 consecutive QC results (obtained over the past year) to justify conversion from daily to weekly QC testing of Antibiotic A? Only one QC result for antibiotic A was out of control during the past 20 days on which we tested Antibiotic A and this corrected upon repeat testing."

User QC Ad Hoc WG: Agenda item 2

Answer:
Yes, you have demonstrated satisfactory performance of "daily QC" by obtaining acceptable results from at least 20 consecutive test days and you can now implement weekly QC testing. Consecutive test days", "or Testing with each use" refers to the actual number of days when a QC test is performed; it is not meant to indicate consecutive calendar days. Don't forget to maintain the records for conversion from daily to weekly QC testing indefinitely. The Subcommittee will clarify wording to address this situation in the next editions of the M02 and M07 standards.

User QC Ad Hoc WG: Agenda Item 2

Rationale:
When an antimicrobial agent not previously tested is added to a laboratory's AST battery, it is important to document that the laboratory can obtain accurate and reproducible results for that drug. This is typically done by testing QC strain(s) each day patient's isolates are tested initially and then converting to a weekly QC testing schedule once satisfactory performance with daily testing is documented. The 20-30 day plan or 15 replicate plan is generally used to convert from daily to weekly QC.

If a patient's isolates are tested with the drug infrequently, the number of QC results needed to convert from daily to weekly QC can span many days or weeks. Reproducibility can be assessed prospectively or restrospectively. This scenario represents a robust test of QC strain performance since it is likely that more staff and a greater variety of lots of materials are used for QC testing.

User QC Ad Hoc WG: Agenda item 3

Request for vote: WG Approved 6/0/5 (For/opposed/absent).

Topic:
One QC result out-of-range when performing weekly QC and no obvious error;

Proposal: Ability to use previous weekly QC data from the same lot instead of testing 5 additional replicates (in accordance with statistical 95% random error).

Question based on message received by CLSI:
”I am seeking assistance regarding the following; our laboratory was recently cited during a CAP inspection for not following the CLSI guidelines regarding an unacceptable MIC value for one drug per one QC organism per one instance with weekly QC done for the month of March. Repeat testing on said organism was okay the following day. (Please keep in mind that this was only one instance for one drug on one QC organism; aside from this exception, our weekly controls are typically within expected ranges).”

User QC Ad Hoc WG: Agenda item 3

Proposed Answer (part 1)

QC ranges are established based on multi-lab, multi-lot M23 QC Studies. Ranges are established to include >= 95% of the results. Therefore a small number of (random) out-of-range QC results may be obtained even when the test method is performed correctly and materials are maintained adequately. If the cause of the error can be reasonably determined, corrective action can be taken and satisfactory performance confirmed with a single QC repeat. However, if the cause of the error can't be reasonably determined, additional testing is needed to determine if the cause of the out-of-range result is due to random error, test conditions, or materials.

User QC Ad Hoc WG: Agenda item 3

Proposed Answer (part 2)
The Subcommittee will clarify wording in "Troubleshooting Out-of-Control Results" to Table 3C (or 4F) and modify M02 and M07 standards to provide additional guidance on troubleshooting and corrective action with the next publication. In addition, we will describe 2 alternatives to satisfy the requirement to have 5 QC results to evaluate by allowing use of retrospective QC (if the previous 4 QC results from the same lot of materials was acceptable) and the ability to test up to 3 QC replicates in a single day. These alternatives may detect problems faster and minimize cost while providing the same level of confidence in confirming acceptable performance.

(Note: rationale is given in text)
See two examples on next page to be published with the Q & A, and included in subsequent M2 and M7 QC sections

User QC Ad Hoc WG: Agenda item 3

Scenario #1
Ampicillin E. coli ATCC 25922 Acceptable Range: 2-8 µg/ml

Week	Day	Lot #	Result	Action
1	1	3564	4	
2	1	3564	8	
3	1	3564	8	
4	1	3564	16	Out of range. Repeat QC same day.
5	2	3564	8	In range. 5 acceptable in range QC tests for E. coli ATCC 25922 and ampicillin with lot 3564. Resume weekly QC testing.

Conclusion: Random QC error

Scenario #2
Ampicillin E. coli ATCC 25922 Acceptable Range: 2-8 µg/ml

Week	Day	Lot #	Result	Action
1	1	9661	4	
2	1	9661	8	
3	1	9661	16	Out of range. Repeat QC same day.
3	2	9661	8	In range. 3 acceptable in range QC tests for E. coli ATCC 25922 and ampicillin with lot 9661. Repeat QC 2 more consecutive days.
3	3	9661	8	In range.
3	4	9661	8	In range. 5 acceptable in range QC tests for E. coli ATCC 25922 and ampicillin with lot 9661. Resume weekly QC testing.

Conclusion: Random QC error

QC testing recommendations for β lactam and carbapenem inhibitor combinations

- References
  - 2 _2013 June Summary of new B lactam QC.pdf
  - 4_QC tables M100-S23 proposed revisions.pdf
  - Tab F, M100-S24, page 140
- Current recommendations: *E. coli* ATCC 35218 as routine and *K. pneumoniae* ATCC 700603 as supplemental
- Recently approved QC ranges for MICs with many antimicrobial agents with *K. pneumoniae* ATCC 700603

QC testing recommendations for β lactam and carbapenem inhibitor combinations

- For avibactam combinations - *K. pneumoniae* 700603 (ESβL organism) is needed for adequate QC.
  - Compound active against TEM1 which is contained by E. coli 35218
  - Will propose *E. coli 35218* as supplemental and K. pneumoniae as routine QC in 2015 publications (projected timing for avibactam combitnation availability). WG approved 7/0/4.
- For other β lactamase/β lactamase inhibitor combinations both QC strains adequate
  - Will revise recommendations (e.g., both acceptable, replace *E. coli* 35218 with *K. pneumoniae* 700603)
  - Request inclusion of disks with *K. pneumoniae* 700603 in future studies?
- Plan text/table clean up to in 2014
  - Revise/combine statement about testing QC org with single drug to ensure org hasn't lost plasmid (footnotes b-e Table 3A,b-f Table 4A)
  - Revise Appendix for QC orgs
  - Update Troubleshooting Guide with all QC strain/antimicrobial agents

QC Working Group Proposal: Evaluate the need for 20-30 day QC testing prior to implementing a new drug for susceptibility testing.

Christopher Doern, PhD, D(ABMM)
University of Texas Southwestern Medical Center

On behalf of the Clinical Laboratory Practices Committee

5 0_CLSI QC WG Project Proposal and Preliminary Data.pdf

Proposal

Background - The CLSI M2/M7/M100 documents state that 20-30 day QC (or 15 replicate plan) must be performed prior to implementing a new drug for patient testing.

Objective – Collect a 20-30 day dataset for disk diffusion validations from multiple institutions and assess QC errors during those studies.

Hypothesis – Most meaningful QC failures will happen in the early phases of testing and further testing is unnecessary.

Preliminary Data/Future Plans

- Solicited disk diffusion validation data for any bug/drug combination.
- Data collection is ongoing but suggest low failure rate.
  - 6 total QC failures occurred over a total of >1,800 data points (2 institutions).
- QCWG suggestions for additional information
  - Experience when adding new drug (frequency of problems/success, cause of issues, # of replicates that would have detected problem)
  - Data may also be helpful for Tier 3 monitoring/reassessment

QC Text/Table Review

- Comprehensive review for Jan 2014 (2015 publication)
  - Request for volunteers
- Table 2:
  - Routine vs Supplemental
- Table 3A and 4A (QC acceptable ranges)
  - Routine vs Supplemental
  - Revise/combine footnotes
  - Consider separate sections for those with no breakpoints
- Appendix C
  - Routine vs Supplemental
  - Revise/combine footnotes
- Troubleshooting Guide
  - Add other drugs with ranges to *E. coli* 35218 and *K. pneumoniae* 700603 to statement about loss of plasmid
  - Add *K. pneumoniae* ATCC BAA1705 with similar comments for carbapenem inhibitor combinations
  - Other revisions for Jan 2014?

Tier 3 QC Review and Plans

- References
  - 1 1_QC Tier 3 Data_2013.pdf
- Reviewed data available to determine if signal warranted further action.
  - Signal <5% out of range: monitor
  - Signal >5% out of range: get Tier 2 data, collect data <3 yrs old, reassess
  - Signal >5% out of range, Tier 2 available, sufficient data: propose revision
- Will request recent data and review in Jan 2014
- Ad Hoc groups to review data then make recommendations January 2014
- Teicoplanin discussion/plans
  - Draft 3 teicoplanin distributed just prior to meeting with original Tier 2 data.
    - Adds M23 Tier 2 data from 1986 and similar 1991 study (blue)
    - Highlighted data without pluronic (purple).
  - Draft 4 with corrections reviewed in QCWG (errors in data entry in draft 3)
  - Clarified position on use of surfactants
    - Original Tier 2 Study most likely included surfactant in inoculum
    - Previous concerns about use of surfactant with teicoplanin primarily referred to preparation of stock solutions and panels.
    - Teicoplanin not as sticky as colistin and televancin (doesn't need surfactant when making stock solutions and panels)
    - Use of surfactant in inoculum some impact (lower shift).
  - QCWG recommends teicoplanin range change to 0.12 – 1 (current 0.25 -1) to be formally voted on in January 2014 after proper review or data.
    - Separate data with and without surfactant and identify the amount of surfactant in MIC well

Tier 3 QC Data/Action Plans

QC Strain (ATCC)	Antimicrobic	Method	Current Range	Action Recmd	Concern
P. aeruginosa 27853	Cefepime	Disk	24-30	Get original M23, reassess	Out high
H. influenzae 49247	Cefepime	Disk	25-31	Monitor	Out high
S. pneumoniae 49619	Cefepime	Disk	28-35	Monitor	Out high
E. coli 25922	Meropenem	Disk	28-34	Get original M23, reassess	Out high
K. pneumoniae 700603	βlactam/βlactamase inhibitors	Disk	No range	Monitor	Alternative for E. coli 35218
E. coli 25922	Cefixime	Disk	23-27	Get original M23, need addn data	Out low
E. coli 25922	Ampicillin	Disk	16-22	Better troubleshooting or reassess QC range	Out low, some double zones

Tier 3 QC Plans/Data Request

QC Strain (ATCC)	Antimicrobic	Method	Current Range	Action Recmd	Concern
P. aeruginosa 27853	Etrapenem	MIC	2-8	Monitor	Out low
E. faecalis 29212	Teicoplanin	MIC	0.25-1	Recommend 4 dil range 0.12-1 based on original Tier 2 and current Tier 3 combined. Will pursue in Jan 2014	Mode from Tier 2 0.12, Tier 3 0.5 w/o surfactant. Shift lower with some media. 9% out low with current range.
S. aureus 29213	Minocycline	MIC	0.06–0.5	Request data/feedback	Mode at low end regardless of read time 16-20 hr
E. faecalis 29212	Minocycline	MIC	1–4	Request data/feedback	Mode at low end at 16 hrs, bimodal at 18 hrs, at middle of range at 20 hrs

Tier 3 QC Plans/Data Request

QC Strain (ATCC)	Antimicrobic	Method	Current Range	Action Recmd	Concern
K. pneumoniae 700603	Ceftazidime	MIC	>16	Monitor/collect data	Verbal reports of some MICs at 16 from one lab
B. fragilis 25285	Pip/tazo	Agar MIC	0.12-1	Monitor	Out low (control M23 study Jan 2010)
H. influenzae 49247	Tigecycline	MIC	0.06-0.5	Monitor	Out high
S. pneumo 49619	Meropenem	MIC	0.06-0.25	Monitor	Bi-modal 0.06 to 0.12.
S. pneumo 49619	Cefuroxine	MIC	0.25-1	Request data/feedback	Mode at 0.25

Thanks to QCWG and User QC Ad Hoc Working Group for efforts between meetings.

If interested in volunteering on one of the Ad Hoc groups for 2014 meetings, contact Sharon Cullen and Steve Brown