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Summary Minutes
Subcommittee on Antimicrobial Susceptibility Testing
Arlington, Virginia
14-16 June 2015

A meeting of the CLSI Subcommittee on Antimicrobial Susceptibility Testing was held on 14-16 June 2015, at the Renaissance Arlington Capitol View Hotel, Arlington, Virginia. The following were in attendance:

Jean B. Patel, PhD, D(ABMM) **Chairholder**	**Centers for Disease Control and Prevention**
John Rex **Consensus Committee on Microbiology** **Vice Chairholder**	**AstraZeneca Pharmaceuticals**
Richard B. Thomson, Jr., PhD, D(ABMM), FAAM **Consensus Committee on Microbiology** **Chairholder**	**Evanston Hospital, NorthShore University HealthSystem**

Members Present

George M. Eliopoulos, MD	Beth Israel Deaconess Medical Center
Stephen G. Jenkins, PhD, D(ABMM),F(AAM)	Weill Cornell Medical Center/NYPH
James S. Lewis, II, PharmD	Oregon Health & Science University
Brandi Limbago, PhD	Centers for Disease Control and Prevention
David P. Nicolau, PharmD, FCCP, FIDSA	Hartford Hospital
Robin Patel, MD	Mayo Clinic
Mair Powell, MD, FRCP, FRCPath	MHRA
Sandra S. Richter, MD, D(ABMM)	Cleveland Clinic
John D. Turnidge, MD	Australian Commission on Safety & Quality in Healthcare
Melvin P. Weinstein, MD	Rutgers Robert Wood Johnson Medical School
Barbara L. Zimmer, PhD	Beckman Coulter Microscan

Advisors Present

Jeff Alder	Bayer
Patricia A. Bradford, PhD	AstraZeneca Pharmaceuticals
William B. Brasso	BD Diagnostic Systems
Rafael Canton	EUCAST/ESCMID

Michael N. Dudley, PharmD,FIDSA	The Medicines Company/Rempex Pharm
Graeme Forrest	Portland VA Healthcare System
Marcelo F. Galas	National Institute of Infectious Disease
Howard Gold	Beth Israel Deconess Medical Center
Dwight J. Hardy, PhD	University of Rochester Medical Center
Janet A. Hindler, MCLS, MT(ASCP)	UCLA Medical Center
Romney M. Humphries, Ph.D., D(ABMM)	UCLA David Geffen School of Medicine
Amy J. Mathers, MD	University of Virginia Medical Center
Tony Mazzulli, MD, FRCPC, FACP	Mt. Sinai Hospital, Toronto
Linda A. Miller, PhD	GlaxoSmithKline
Sumathi Nambiar, MD, MPH	FDA/CDER
Helio S. Sader, MD, PhD	JMI Laboratories
Michael Satlin, MD, MS	Weill Cornell Medical College
Paul C. Schreckenberger, PhD, D(ABMM), F(AAM)	Loyola University Medical Center
Audrey Schuetz, MD, MPH, D(ABMM)	Weill Cornell Medical Center/NYPH
Susan Sharp, PhD, D(ABMM)	Kaiser Permanente-NW/ASM Representative
Ribhi M. Shawar, PhD, D(ABMM)	FDA Ctr. for Devices/Rad. Health (CDRH)
Kerry Snow	FDA
Pranita D. Tamma, MD, MHS	Johns Hopkins University School of Medicine
Maria M. Traczewski, BS, MT(ASCP)	The Clinical Microbiology Institute

Reviewers Present

Paul G. Ambrose, PharmD, FIDSA	ICPD
Robert Badal	IHMA, Inc.
Sujata M. Bhavnani, PharmD	ICPD
Lynn Boyer	Beckman Coulter
Steven D. Brown, PhD, ABMM	Consultant
Karen Bush, PhD	Indiana University
Laurent Chesnel, PhD	Merck
Diane M. Citron, M(ASCP), BS	R.M. Alden Research Laboratory
Patricia S. Conville, MS, MT(ASCP)	FDA/CDRH
Ian Critchley, PhD	PharMicro Consulting
Sharon K. Cullen, BS, RAC	Beckman-Coulter
Michael J. Dowzicky	Pfizer Inc
German Esparza, BSc	Proasecal sas colonbio
Robert Eusebio, MSHA, MT(ASCP)	Beckman Coulter
Gina L. Ewald-Saldana, CLS(CA), MT(ASCP)	Beckman Coulter
Robert K. Flamm, PhD	JMI Laboratories
Mary Jane Ferraro, PhD, MPH	Harvard Massachusetts General Hospital
Lawrence V. Friedrich, PharmD	Merck
Barb Gancarz	bioMerieux, Inc.
Beth P. Goldstein, PhD	Beth Goldstein Consultant
Patricia Hogan, MT(ASCP), MBA	Pfizer Inc

Denise Holliday`	BD
Michael D. Huband	JMI Laboratories
Jack L. Johnson	IHMA, Inc.
Scott B. Killian	Thermo Fisher Scientific
Susan Kircher, MS, MT(ASCP)	BD Diagnostic Systems
Cythia C. Knapp, MS	Thermo Fisher Scientific
Laura M. Koeth, MT(ASCP)	Laboratory Specialists, Inc.
Peggy Kohner	Mayo Clinic
Sarah Blaine Leppanen	Blaine Healthcare Associates Inc.
Dyan Luper, BS, MT(ASCP)SM	BD Diagnostic Systems
Maureen Mansfield	Thermo Fisher Scientific
Susan D. Munro, MT(ASCP)	Consultant
Susan O'Rourke	BD
Linda Otterson	Independent Clin Microbiologist
Elizabeth Palavecino, MD	Wake Forest University Baptist Medical Center
James A. Poupard, PhD	Independent consultant
L. Barth Reller, MD	Duke University Medical Center
Robert P. Rennie, PhD	R. P. Rennie Consultation, LtD
Darcie E. Roe-Carpenter, PhD, CIC, CEM	Beckman Coulter Microscan
Dale A. Schwab, PhD, D(ABMM)	Quest Diagnostics, Nichols Institute
Katherine Sei	Beckman-Coulter
Janine Spafford	BD
Judith N. Steenbergen, PhD	Merck
Laura Stewart	BD
Jana Swenson	
Lauri D. Thrupp, MD	University of California Irvine Medical Center
Nancy Watz	Stanford Hospital and Clinics
Matthew A. Wikler, MD, MBA, FIDSA	
Vicki Whitley	BD
Mary K. York, PhD, ABMM	MKY Microbiology Consulting

<u>Observers Present</u>

Erica Alberson	bioMerieux, Inc.
Diane Anastasiou	Merck
Stella Antonara	Nationwide Children's Hospital
Eliana Armstrong	
Mary Arndt	Beckman Coulter Microscan
Adam Belley, PhD	The Medicines Company
April Bodenchik	Lifespan/Rhode Island Hospital
Linda C. Bruno, MA, MT(ASCP)	ACL Laboratories
Deb Butler	GSK
Boudewijn de Jonge	AstraZeneca
Dana Dressel	IHMA, Inc.
Glenn Enscoe	Beckman-Coulter

Sheila Farnham, MT(ASCP)	bioMerieux
Christine Hastey	Beckman Coulter
Nicole Holliday	Thermo Fisher Scientific
Ann Howell	Shionogi Inc
Jocelyn Jennings	bioMerieux, Inc.
Ron Jones, MD	JMI
Nachum Kaplan	Nobelex Biotech
Roberta E. Knefel	bioMerieux. Inc.
Xian-Zhi Li, PhD	Health Canada Veterinary Drugs
Ron Master	Quest Diagnostic
Shelly Miller	UCLA
Greg Moeck, PhD	The Medicines Company
Timothy Morris	Actelion Clinical Research
Ross Mulder, MT(ASCP)	bioMerieux, Inc.
Mark Needles	FDA/CDER
Paul Newell	AstraZeneca
Kiyofumi Ohkusu	Tokyo Medical University
Chris Pillar	Microruyx
Angela Prouse	Peninsula Regional Medical Center
Janet Raddatz	Cubist
Kerian Grande Roche	FDA/CDER
James Ross	JMI Labortories
Markus Rose, DVM, PhD	Merck Animal Health
Nicole Scangarella-Oman	GlaxoSmithKline
Charles Schraa	Actavis PLC
Alisa Serio, PhD	Achaogen
Carole Shubert	bioMerieux, Inc.
Simone Shurland	FDA, CDER
Jennifer Smart	Theravance BioPharma
Andrea Saigol	Accelerate Diagnostic
Jacal Sheikh	FDA/CDER
Kileen Shier	Quest Diagnostics
Kalavati Suvarna	FDA/CDER
Kazuhiro Tateda, MD, PhD	Toho University
Susan Thomson	MAST Group
Masakatsu Tsuji, PhD	Shiongi & Co. Ltd
Yoshinori Yamano, PhD	Shionogi & Co. Ltd
Katherine Young	Merck

CLSI Staff

Tracy A. Dooley, BS, MLT (ASCP)
Glen Fine, MS, MBA, CAE
Marcy Hackenbrack, MCM, M(ASCP)
Stephanie Robinson

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I. MEETING/OPENING REMARKS

Dr. Jean Patel called the meeting to order at 1:00 p.m. on Monday, 15 June 2015. She welcomed everyone and thanked all the working groups (WG) for the all the on-going work being done outside of the January and June meetings. All of the WGs have been busy over the past few months, accomplishing much of the work thru conference calls and e-mail, making this meeting more efficient. She then recognized the achievements of three WGs in particular:

- M45 WG led by Dr. Sandy Richter and Ms. Janet Hindler. This WG has done a tremendous job on the significant updates made in the M45 document that is estimated for publication in September.

- M23 WG led by Dr. Mair Powell and Mr. Kerry Snow along with the PK/PD WG lead by Dr. Linda Miller. These two WGs have also made significant updates to the M23 document to align it with the AST Subcommittee's new processes. Currently the M23 document is out for subcommittee comment and member vote and Dr. Patel encouraged everyone to review the draft and submit any comments they may have.

Dr. Patel acknowledged and thanked the following new Recording Secretaries and WG liaisons for the assistance that they provide:

- Dr. Melissa Miller is the new recording secretary for the Methodology WG
- Dr. Carey-Ann Burnham is the new recording secretary for the Text & Tables WG
- Mr. Jim Ross is the new recording secretary for the Quality Control WG
- Drs. Sandy Richter and Darcie Roe-Carpenter – Methodology WG liaisons to T&T WG
- Drs. Barb Zimmer and Audrey Schuetz – Breakpoint WG liaisons to T&T WG

She introduced Dr. Graeme Forrest, who is an Associate Professor of Medicine at Oregon Health and Science University. Dr. Forrest is a new advisor on the subcommittee.

Dr. Patel then reminded everyone the purpose of this subcommittee is to develop standards for antimicrobial susceptibility testing for laboratories. These standards help ensure accurate testing for improved patient care.

Dr. Tom Thomson, Chairholder of the Consensus Committee on Microbiology made the subcommittee aware of the recent approval of the document M52, *Verification of Commercial Identification and Antimicrobial Susceptibility Testing Systems*. This document will be prepared for publication and available in July.

II. CLSI UPDATE

Mr. Glen Fine, CEO of CLSI welcomed everyone and thanked the Subcommittee for their continued work. He then presented CLSI Excellence in Standards Development Awards to the following recipients:

- Dr. Mary York who has been an active volunteer and participant of the AST Subcommittee, has been involved as a member of various WGs over the years including the Text & Tables WG. As a

microbiology consultant, Dr. York has tirelessly promoted the use of CLSI standards and guidelines, promoting the Subcommittee's mission of ensuring accurate testing for improved patient care.

- Dr. Karen Bush is an internationally recognized expert in microbial resistance who has participated on the AST Subcommittee since 2002. She has served as a voting member, an advisor, as well as Chairholder of three various WGs. Over the years she has continually provided her expertise while continually mentoring our new generation of volunteers.

III. UPDATES TO THE CURRENT AST DISCLOSURE SUMMARY

Dr. Patel asked the members and advisors for any updates to the current disclosure summary provided on the CD of meeting materials – Dr. George Eliopoulos provided updates that will be added to the summary.

IV. APPROVAL OF THE JANUARY 2015 MEETING MINUTES

Summary minutes of the 11-13 January 2015 subcommittee meeting were approved: **(11-0)**

V. REPORT OF THE METHODOLOGY WORKING GROUP (Electronic Folder 5)

Co-Chairholder - Brandi Limbago
Co-Chairholder - Stephen Jenkins

Members Present: Bill Brasso**,** Romney Humphries, Joe Kuti, Sandra Richter (Text & Tables Liaison), Darcie Roe-Carpenter (Text & Tables Liaison), Katherine Sei, Susan Sharp, Ribhi Shawar, John Turnidge

Technical Advisor Present: Laura Koeth

Members Absent: Melissa Miller, Recording Secretary

1. **Introduction of Group and New Members.**

2. **Discussion of methodologic path forward for new agents not compatible with current reference method (Shionogi)**

   Background: New agent S-649266 does not yield with the appropriate MIC which has a good relationship with *in vivo* efficacy by using reference broth microdilution using CAMHB for all species . Agent requires iron-depleted media to obtain reliable MIC results which reflect well with *in vivo* efficacy. When iron-depleted CAMHB was used, a reproducible MIC was not obtained, particularly for *Acinetobacter* spp. due to trailing phenomenon.

   At the January 2015 CLSI meeting, Shionogi presented data that an alternate standardized media (Isosensitest broth; ISB) treated with Chelex (ch) chelator performed well for broth microdilution.

However, chelex is proprietary and available from only one manufacturer, and ISB is available from only one manufacturer.

QC ranges for testing with CAMHB were approved.

In April 2015, a teleconference between Shionogi and the Methods WG was held. We discussed criteria that would be necessary for alternate reference methodologies to be deemed acceptable, and requirements for such methods. We also discussed the fact that agar dilution appears to work well, so it might be considered for use as a reference method.

At this meeting: Data presented for CAMHB treated with various chelators, including Chelex. Sponsor described plans going forward for:

1) a QC study evaluating 3 lots CAMHB from at least two manufacturers;
2) a reproducibility study for CAMHB and chMHB.

There was a discussion about the appropriate guidance for the MIC determination against the strains showing trailing phenomenon. It was recommended to define the appropriate guidance to determine the reproducible MIC even when the trailing occurs.

There was discussion about the use of various chelators and methods for producing chCAMHB, as well as the use of different reference methods (broth and agar dilution) for *Enterobacteriaceae* and *Acinetobacter* spp. It was recommended from a device manufacturer that a performance standard (e.g., iron-depleted CAMHB containing specific concentrations of Ca^{++}, Mg^{++}, Zn^{++}, plus a maximum or range for an acceptable concentration of Fe) would be a more reliable standard, and would circumvent concerns about which specific chelator was used to achieve this standard.

Motion from Methods WG: Encourage the sponsor to move forward with a modified version of Proposed Plan 2, using a performance a standard rather than a methodologic standard. The WG would be interested in seeing photos of the results (i.e., trailing) to determine whether a single reference method with specific reading guidance could be developed.
WG Vote: 9 in favor; 0 opposed

Subcommittee Vote – the Subcommittee agreed with the Motion from the Methods WG eg, using a performance a standard rather than a methodologic standard – **Approved 11-0**

Further comment from Methods WG: If broth microdilution method cannot be used as the reference for *Acinetobacter* spp., agar dilution would be an acceptable alternative.

3. Presentation from Cubist/ Merck

Discussed implications of text in CLSI document M07 regarding linezolid and trailing endpoints, to better understand the implication of the text since both tedizolid and linezolid are members of the oxazolidinone class.

Sponsor recommends adding tedizolid to the list of drugs for which trailing should be excluded when reading growth and assessing endpoints; presented data from QC strains tested at several laboratories that guidance re. ignoring trailing results at lower MICs.

a. WG Vote: Approved inclusion of tedizolid in trailing endpoint verbiage as proposed by sponsor for M7-A11 (9/0/0)
b. Recommended inclusion of a comment in next edition of M100 explaining the trailing and how to read results in such cases (9/0/0) – refer to item #3 under the Report of the Text and Tables Working Group for the new comment to be added to gram-positive tables 2C, 2D, 2G, 2H-1 and 2H-2.
c. Sponsor agreed that a new QC study would be required to see whether multiple laboratories/readers can generate comparable results based on such instructions
   - Photos of findings would be taken for potential inclusion in a subsequent version of M7

Subcommittee Vote – the subcommittee agreed to the recommendation of the WG shown above **(Approved 11-0)**

4. Presentation from the Medicines Company re. Oritavancin testing – Adam Belley

BMD QC strain, ATCC® 25923, has an oritavancin MIC in the resistant range (1 dilution above the 0.125 µg/mL breakpoint), and as such is not an ideal QC strain. The sponsor requests that ATCC® 29213, an alternate QC strain and one that is used routinely for the β-lactamase test, be recommended when testing oritavancin.

Also, presented data that addition of the surfactants Polysorbate-80 and Span-80 to oritavancin disks produced much more reproducible zone sizes for disk diffusion testing. Sponsor requests that disk diffusion method for oritavancin testing include both P-80 and Span-80.

Discussion around 1) use of two wetting agents in disks, 2) acceptability of ATCC® 29213 as QC strain, and 3) utility of this strain vs. ATCC® 25923 for identifying media that does not pass QC

Motion from Methods WG: For oritavancin testing, disks containing P-80 and S-80 should be used; QC strain should be ATCC® 29213 – **WG** Vote**: 9/0/0**

Subcommittee Motion: The Subcommittee agreed with the recommendations from the WG – **Approved 11-0.**

5. Report from the BMD Ad Hoc WG – Bill Brasso, Chair

Bill reviewed actionable survey questions from the January 2015 meeting. Based upon January 2015 survey results, presented our recommendations to control the amount of variability for several steps in broth microdilution testing, and requested a vote from the AST SC and Text & Tables WG for several of these for incorporation into M07. Seven recommendations were proposed:

1. Insure method used to adjust McFarland is verified. WG decision: **No vote**. A clarifying statement is not needed since instrument manufacturers provide instructions with their products. Withdrew recommendation.
2. Need to clarify in M07 when colony counts are required. Much discussion**. No decision** for the WG at this time.
3. Insure incubator temperature is within M07 recommendations of 35 +/- 2°C, or should we switch to ISO 34 - 37°C? **WG decision: No vote**. Leave at 35 +/- 2°C.
4. Need to include a range of time to thaw panels at room temperature, and clarification on stacking panels in M07. Much discussion. **WG vote**: 6/3/1 in favor of including a statement that 'panels should be thawed no longer than 1hour at room temperature and not stacked', but WG asked for data. B. Badal has agreed to provide IHMA data for next meeting.
5. How to interpret difficult endpoints? **WG decision**: supportive, but need to bring recommendations and pictures to Text & Tables.
6. How to better define valid growth in Growth Control well. **WG is supportive**, but asked the group to work on a statement.
7. Add pictures and statements to M07 on how to interpret skipped wells. **WG is supportive**, but asked the group to work with Text & Tables.

Several other items were discussed for information only, and not requesting a vote.

Informational presentations on variability in BMD method:

1. Katherine Sei presented slides showing that even strict adherence to the CLSI recommended parameters does not prevent variable results. Even when conditions are managed well, the isolate and drug combination appears to be a significant contributor to variation ('Random induction' of β-lactamase production cannot be controlled)
2. David Nicolau (Hartford Hospital) provided slides of clinical isolates and various antibiotics tested multiple times in his laboratory. He concluded that many drug/ organism combinations provide very consistent MICs, but others vary widely. Possible causes include enzyme-mediated resistances, trailing, and reader to reader differences.
3. Michael Ullery provided slides demonstrating with a fairly large data set and simulations of that data that 1) > 75% of the drug/organism combinations tested produced more than one MIC when tested multiple times (~ 25% produced 3 or more MICs); therefore, it's unrealistic to think of many organism/drug combinations as having a single MIC, and 2) with this in mind, we cannot expect more precision from our reference BMD method.

During presentation to the full SC, enthusiastic discussion arose. Among those who provided comments, Brandi suggested that we may want to investigate each source of variability. We "may be as tight as it will get", knowing you can't improve variability. Tom Thomson asked, "Can we do something with the report; e.g., modify an S result near a breakpoint, such that pharmacy knows?" This was deemed an "important issue." Team plans to bring recommendations based on these data and follow-up discussions to Methodology WG at January meeting for a vote

6. Report from Alternate Disk Mass Ad Hoc WG – Laura Koeth, Chair

- EUCAST has recommended disks with lower disk mass because they have found evidence that lower disk mass performs better for separating S from R with disk diffusion. CLSI would like to harmonize methods. This would help with efforts for global AR surveillance by WHO.
- Discussion ensued as to whether lower disk contents may be needed when breakpoints are lowered (eg, the cephalosporins as linearity is seen near the 8 µg/mL breakpoint with the 30 µg disk)
- In general, participants of the WG indicated that the disk mass should only be changed if the accuracy of the test is significantly improved. Participants also noted that:

  – A M23 study would be required and funding for this was unclear; could EUCAST data be used instead of generating new data?
  – M23 guidance for disk mass change is vague
  – A change would affect drug labels
  – It would be unfavorable to have two different mass disks for the same drug

- The WG discussed a plan to evaluate the need to change disk mass by reviewing scattergrams available from CLSI old records and comparing these to EUCAST scattergrams generated with lower disk content

  – Cefotaxime, ceftaroline, ceftazidime, linezolid, netilmicin, penicillin, piperacillin, piperacillin-tazobactam
  – Concerns: sometimes the EUCAST MIC result could have been generated with Etest; however EUCAST data is peer-reviewed in committees, in a way similar to CLSI

- Comments:
  – Cephalosporins are major issue; drugs have widely varying potency and thus really should have different masses

7. Report from Tables 1 & 2 Clean-up Ad Hoc WG – Mary York, Chair

Charge – delete discontinued drugs from Table 1 and resolve discrepancies

– Committee verified that loracarbef, spectinomycin & dirithromycin have been discontinued

– Also, ticarcillin-clavulanate is no longer manufactured by GSK (and not by anyone else)
– Piperacillin no longer available (but piperacillin-tazobactam is); suggest to move Piperacillin-Tazobactam to Group A

Items for vote:

a. Remove loracarbef, spectinomycin, dirithromycin from Table 1 (unanimous from ad hoc group)
   - WG Vote: 9 in favor; 0 opposed; 1 abstained
   - **Subcommittee Vote: Approved - 9-0; 2 absent**

b. Remove ticarcillin-clavulanate because it has been discontinued
   - Still FDA-approved drug
   - Will not be available for testing for long
   - Was this contentious among ad hoc group?

   Methods WG Motion to move to group C: 6 in favor; 3 opposed; 2 abstained
   (Opposed- think that there are many drugs that could go to C with this rationale)

   - Subcommittee Motion to move ticarcillin-clavulanate to group C. **Subcommittee Vote: 3-6; 2 absent – Not Approved.**

   - Subcommittee - 2nd Motion to remove ticarcillin-clavulanate from Table 1 (leave in Table 2 – moves to Test/Report Group O): **Subcommittee Vote: Approved 7-2; 2 absent**

c. Remove piperacillin from Table 1. For *P. aeruginosa* move piperacillin-tazobactam to Group A (unanimous from ad hoc group)
   - WG Vote: 9 in favor; 0 opposed; 1 abstained
   - **Subcommittee Vote: Approved 9-0; 2 absent.**

d. Additional information- There had been a request to change the *Acinetobacter* group to *Acinetobacter baumannii* complex in the document tables; the group recommends against it (unanimous from the ad hoc group)

   – Previous recommendation from Methods WG because it was so difficult to assign antibiotics to groups A, B, C
     - WG Motion: leave table as is (*Acinetobacter* species) - 8 in favor; 1 opposed; 1 abstained
     - **Subcommitte Vote to keep table as *Acintobacter* spp. - Approved 8-1; 2 absent**

e. *Acinetobacter* spp.: propose to delete cefotaxime, ceftriaxone, tetracycline (Group B) from Table 1

- So moved. WG Vote: 4 in favor; 3 opposed; 3 abstained – Does not pass
- WG - 2nd motion: remove cefotaxime and ceftriaxone; **move tetracycline to group U**
- WG Vote: 6 in favor; 0 opposed; 4 abstained – does this pass?

- **Subcommittee Vote:** For Acinetobacter spp./tetracycline, move from Test/Report Group B to Group U- **Approved 9-0; 2 absent**

  Note: To remove cefotaxime and ceftriaxone from *Acintobacter* spp. Test/Report Group B was not voted on previously by the Subcommittee as initially thought (see January 2015 minutes) and will be reviewed/discussed at the next meeting.

f. Chloramphenicol – move to group C each time it is cited (*B. cepacia* complex, *S. maltophilia*, and *H. influenzae* and *H. parainfluenzae*)
   - WG Vote: 8 in favor; 0 opposed; 1 abstained
   - **Subcommittee Vote: Approved 8-0; 3 absent**

g. Place polymyxin B (PB) and colistin in group C for *Acinetobacter* spp.
   Discussion – only available as BMD method, only RUO tests for agar

   - Motion: Put PB & colistin into group C for *Pseudomonas* and *Acinetobacter*, modified to be colistin ONLY into group C, Table 1
   - WG Vote: 6 in favor; 1 opposed; 3 abstained

   - **Subcommittee Vote: add colistin to group C for *Pseudomonas*: <u>Not Approved</u> – 5-4; 2 absent. No Change.**

h. Move meropenem to Test/Report Group A for *Burkholderia*
   - WG Vote: 7 in favor; 0 opposed; 2 abstained
   - **Subcommittee Vote: Approved 8-0; 3 absent**

i. Delete erythromycin from Table 1 for viridans group streptococci; not appropriate for therapy (unanimous from ad hoc group)
   - No motion from WG
   - **Subcommittee: Not discussed – No change.**

j. Remove quinupristin/dalfopristin from *Streptococcus* spp. β-Hemolytic Group
   - Not in Table1 for *S. aureus*; not a good drug for its indication; not often available
   - WG Vote: 7-0-3 (1 absent)
   - **Subcommittee Vote: Approved 7-1; 3 absent**

k. Move drugs from groups B and C to group A

Discussion: Leave ampicillin in A; move trimethoprim-sulfamethoxazole (SXT) to group B; remove all drugs from group B; remove most drugs from group C (only chloramphenicol, azithromycin, clarithromycin, rifampin, and tetracycline would remain). Options to leave some drugs with S-only breakpoint for CSF. Would include footnotes

- WG Discussion: SXT needed for penicillin-allergic patients

- Move everything out of Group B

1. No motion to move SXT out of group A
2. No motion to move any drugs out of group B
3. No motion to make changes to group C
4. Motion: add 'May' language to Group B short descriptions
5. Vote: 9/ 0/0

Subcommittee: Not discussed – No Change

8. Report from Anaerobe Ad Hoc WG – Darcie Carpenter, Chair

- Epidemiologic cutoff values (ECV) for vancomycin and *Clostridium difficile*

Ad hoc group collected and summarized 2810 data points; recommended cut-off of 4 µg/mL.

– EUCAST data was reviewed; noted EUCAST peak at 0.5 µg/mL; ad hoc group data peak is 1 µg/mL
– Also noted, EUCAST ECOFF at 2 µg/mL. It was also noted that the testing method is unknown for the EUCAST data. WG data is using current isolates recovered within the last three years.
– Ad hoc group wants to look at older data. It was noted that the 027 strains are more resistant than other types. Data could be skewed due to over-representation of these strains; therefore, the ribotype should be added to the old and current data. Ad hoc group will try to collect this data to review and discuss for the January 2016 meeting.

- Epidemiologic cut-off values (ECV) for vancomycin vs. gram-positive anaerobes
Ad hoc group will continue to collect data to support an ECV for vancomycin and gram-positive anaerobic species. Will review for January 2016 meeting.

- Draft Publication Review

Ad hoc group discussed the approach of the publication and the presentation of the data in the manuscript; recommended keeping all of the data in the manuscript and waiting for editorial comments. It was also recommended to keep as close as possible to the data tables in M100, and to again wait for editorial comments.

- Agar vs. Broth data

  Ad hoc group members will have more data later in the year for discussion at January 2016 meeting

- Review update for M11 document (June 2014)

  A plan forward for revisions has been determined; however, the ad hoc group does not want to publish another revision of M11 until the agar vs. broth discussion is complete.

  – Individual edits are due at the end of September; Darcie will compile and send out.
  – Conference call to be scheduled middle of October to discuss.
  – Final draft will be included in the agenda book for the January 2016 meeting.

- *Eggerthella lenta* required use for Quality Control

  E. lenta is not a good QC organism for some antimicrobial agents. Also, historically *C. difficile* was added as a QC organism to address this issue.

  – Ad hoc group recommends NOT requiring that *E. lenta* be used in M23 studies for new antimicrobial agents when organism performance issues are known.

  – Ad hoc group recommended additional wording be added to M100 to provide more clarity regarding this issue. Suggested wording below:

    M100
    Table 5D MIC QC Ranges for Anaerobes (Agar Dilution Method) page 168,
    and
    Table 5E MIC QC Ranges for Anaerobes (Broth Microdilution Method) page 170

    Footnote to the organism:
    "MIC variability with some agents has been reported with *Eggerthella lenta* (*E. lentum*) ATCC 43055; therefore, QC ranges may not have been established for all antimicrobial agents with this organism."
    and
    M100 Appendix C, QC Strains for Antimicrobial Susceptibility Tests page 204
    Added to "Other column" for *E. lenta:*

    "MIC variability with some agents has been reported with *Eggerthella lenta* (*E. lentum*) ATCC 43055. Therefore, QC ranges may not have been established for all antimicrobial agents with this organism and is not required to include in M23 QC Tier 2 studies if MIC result variability is documented in early drug development studies (ie M23 QC Tier1)."

Subcommittee Vote: Approved 9-0; 2 Absent

9. Report from Molecular Results Reporting Ad Hoc WG – Tom Kirn, Co-chair (with Cathy Petti)

Ad Hoc WG Charge: Provide guidance to laboratories that employ molecular methods to detect antibiotic resistance mechanisms when reporting for clinical applications.

- Group defined **molecular** tests as those targeting proteins or nucleic acids; recommended starting with FDA-cleared tests; recommended that this guidance be placed in M100 as Tables, and focus primarily on how to address discrepant results
- WG developed tables resolving discrepancies for *S. aureus*, enterococci, and Enterobacteriaceae
- Guidance from WG:
  - consider expanding to address how clinical laboratories would report gene presence to clinicians;
  - consider working closely with outreach group because this is a large increase in the scope of M100;
  - Robin Patel indicated she would be willing to share the approaches used at the Mayo Clinic for clinical reporting; Darcie Carpenter indicated she would be willing to work with the ad hoc group to address issues of reporting for infection control decisions.

10. Update on ISO documents – Barb Zimmer

- ISO 20776-1 (*Clinical laboratory testing and in vitro diagnostic test systems – Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices – Part 1: Reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases*) currently undergoing periodic review to determine if revision is needed
- ISO 16782 (*Antimicrobial susceptibility testing – Criteria for acceptable lots of dehydrated Mueller-Hinton agar and broth for antimicrobial susceptibility testing*) was approved April 2015; will be published late summer/ early fall

11. Update from Intrinsic Resistance Ad Hoc WG – Barb Zimmer, Chair

Intrinsic Resistance Ad Hoc WG via email reviewed references and voted unanimously to remove the intrinsic resistance "R" for *Pseudomonas aeruginosa* and fosfomycin from Appendix B2, Intrinsic Resistance in Non-Enterobacteriaceae.

Subcommittee Vote: Approved 9-0; 2 Absent

12. Report from Direct AST working group – Romney Humphries, Chair

- Define a standardized methodology for performing AST directly from positive blood culture broth (treatment of sepsis, inform antimicrobial stewardship, provide reference to use for comparison)
  - Would still need to be verified in performing laboratory; would be an laboratory developed test (LDT)
  - Desire to be able to report a 'final' result for direct AST
- Extensive literature review – numerous methods have been used, all with good performance
- Performance review (UCLA data) also looked good
  - 0.5 McFarland standard prepared by direct colony suspension vs. growth method demonstrated differences in viable counts for both gram-negatives and gram-positives, but did not impact the results/ interpretations for disk diffusion (up to 1 log difference had no impact)

- Evaluated CFUs present in positive blood culture bottles (spiked QC strains)
- Next steps: Evaluate direct agar inoculation from positive blood culture bottle without standardization for carbapenem-resistant Enterobacteriaceae (CRE), resistant *A. baumannii*, resistant *P. aeruginosa*, and QC organisms at 3 sites using one media manufacturer; 25 isolates per site

  - Targets: >90% EA, >90% CA, <2% VME, ME; requires >95% QC in control range
  - Currently looking for study sites; hoping that manufacturers will provide blood culture bottles

13. Report of Atypical *S. aureus* group – Romney Humphries, Chair

- Need AST method for atypical *S. aureus* that won't grow in traditional media/ conditions (e.g., small colony variants; auxotrophic isolates)
- Two study phases planned:
  - AST for oxacillin resistance: is PBP2a test reliable? Can BMHA (or other) be used for cefoxitin disk diffusion?
  - AST for other antimicrobials: maybe CAMHB + LHB? Consider evaluating genome?

14. **Report on Testing for Oxacillin Resistance in *Staphylococcus pseudintermedius* – Romney Humphries, Chair**

- *S. pseudintermedius* can be coagulase-positive; may be mis-identified as *S. aureus* in laboratory
  - Uncommon human pathogen, but can occur and cause serious infections
  - *S. pseudintermedius* studies at several sites:
    - With/ without *mecA*, including *mecA* PCR, disk BMD with oxacillin and cefoxitin
  - Oxacillin MIC tests using coagulase-negative staphylococcal breakpoints correlate well with *mecA* presence

- WG Motion to accept the mock-up new Table 2C listing for *S. pseudintermedius* (See Appendix A at end of this minutes)

  WG Vote: 8 in favor; 1 opposed; 1 abstained

  Subcommittee Vote: Approved 6-3; 2 absent

15. Surrogate Testing informational update – Jim Jorgensen, Chair (presented by S. Jenkins and M. Weinstein)

- Group recently formed, met via conference call. Reviewing document assembled by J Hindler that identifies reference to 'surrogate testing'
- Charge of the WG:
  - Define what is meant by surrogate testing
  - Gather information on older and new uses of surrogate test markers
  - To the extent possible harmonize language and usage such as "or" and various comments in the documents
- Background:
  - Some drugs cannot be tested accurately by disk – dalbavancin, oritavancin, tedizolid
  - Some drugs stick to plastic and cannot be tested by E test strips - dalbavancin, oritavancin, tedizolid
  - For those that can be tested by E test, still need FDA clearance (RUOs?)

Why test a surrogate?:

- If testing the surrogate provides a more accurate answer than testing the drug of interest itself (cefoxitin for oxacillin)
- If the surrogate is generalizable to other drugs in the same class (ampicillin for amoxicillin)
- If the surrogate is more readily available or the drug of interest is not available

The below definition was presented to the Subcommittee for consideration:

A surrogate drug can be defined as one that will accurately predict the susceptibility and/or resistance of another antimicrobial agent. Surrogate drugs may predict susceptibility only, resistance only, or both susceptibility and resistance. A surrogate susceptibility test may be useful in several settings.

Examples include:

• For efficiency, if one agent can be tested and those results accurately applied to other members of the same class it may preclude testing of several closely related agents (eg, ampicillin to represent amoxicillin, penicillin G to represent other β-lactamase labile penicillins with staphylococci).

• As indicated in some Tables in the document by the use of "or" between agents, cross susceptibility and resistance among some closely related agents is nearly complete (VME + ME < 3%; mE < 10%) and only one agent need be tested.

• Testing a surrogate may provide more accurate prediction of susceptibility and resistance than testing the agent of interest itself (eg, testing cefoxitin to predict susceptibility to oxacillin with staphylococci, testing pefloxacin and nalidixic acid to detect reduced fluoroquinolone susceptibility in *Salmonella*).

• Testing of a surrogate may be used to detect either susceptibility or resistance to closely related agents that may be technically difficult to test or for which reagents for testing are not readily available (eg, tetracycline susceptibility to predict doxycycline or minocycline susceptibility with some species).

Subcommittee Vote: The Subcommittee approved to add this definition in the next edition of M100 in the Instructions for Use of Tables section – **Approved 9-0; 2 absent**.

16. Unmet Needs

- Typically we report combination drugs with inhibitors that do not have intrinsic activity as a ratio. But, what should we do when they both have activity? e.g., novel compound + meropenem at a fixed 1:1 ratio – data were presented as 1:1 = 2, 2:2 = 4, etc. rather than 1, 2, etc. Just need to decide what the precedent should be going forward

  Our previous precedents:

  Drug plus inhibitor with limited or no antibacterial activity usually 1/1, 2/2, etc.
  Two active components (e.g., trimethoprim-sulfamethoxazole); ratio is different

VI. REPORT OF THE BREAKPOINT WORKING GROUP (Electronic Folder 6)

Co-Chairholder – Dr. George Eliopoulos
Co-Chairholder – Dr. Jim Lewis
Recording Secretary – Dr. Karen Bush

Members Present: Marcelo Galas, Amy Mathers, David Nicolau, Mair Powell, Michael Satlin, Paul Schreckenberger, Audrey Schuetz, Simone Shurland, Lauri Thrupp, Mel Weinstein, Barbara Zimmer

Technical Advisor Present: Matt Wikler

Members Absent: Hui Wang

1) Tedizolid Breakpoint Presentation (See Briefing documents 6.1.0, 6.1.1, 6.1.2)

Presenters: Drs. Mekki Bensacci, Shawn Flanagan and Taylor Sandison.

The sponsor requested that CLSI accept the FDA-approved breakpoints as shown below:

Pathogen	Minimum Inhibitory Concentrations		
	S	I	R
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)	≤0.5	1	≥2
Streptococcus pyogenes	≤0.5	-	-
Streptococcus agalactiae	≤0.5	-	-
Streptococcus anginosus Group[a]	≤0.25	-	-
Enterococcus faecalis	≤0.5	-	-

S=susceptible; I=intermediate; R=resistant

[a]Includes *S. anginosus*, *S. intermedius*, *S. constellatus*

After meeting with the sponsor in a teleconference prior to the WG meeting, the Ad Hoc Working Group, composed of : Jim Lewis (Chairholder), Howard Gold, Audrey Schuetz, and Tony Mazzulli, Jean Patel (Chairholder of AST Subcommittee) and Pranita Tamma, supported publication of breakpoints for tedizolid, and was willing to accept the breakpoints set by FDA.

The Sponsor also requested the following placement of tedizolid in Table 1 of Document CLSI M100.

- For *Staphylococcus* spp. and *Enterococcus* spp. it is recommended that tedizolid be placed in Group B (Primary Test Report Selectively).
- For *Streptococcus* spp. β-hemolytic group and *Streptococcus* spp. (viridans Group) it is recommended that tedizolid be placed in Group C.

The Ad Hoc WG proposed placement of tedizolid in Table 1 of M100-S27 as follows:

- For *Staphylococcus* spp. it was recommended that tedizolid is placed in Group C
- For *Enterococcus* spp. it was recommended that tedizolid is placed in Group C
- For *Streptococcus* spp. β-hemolytic group and *Streptococcus* spp. (viridans Group) it was recommended that tedizolid be placed in Group C.

The Ad hoc WG also proposed the following comment be added for tedizolid in Table 1 and 1A with the drug as well as the appropriate Table 2s:

In an animal model, the antibacterial activity of tedizolid was markedly reduced in the absence of granulocytes and this drug has not been studied in neutropenic patients. In neutropenic patients, tedizolid is not a drug of choice and may not be effective.

Discussion:

1. Why was there no disk diffusion breakpoint requested? The sponsor replied that the disk did not meet expectations and the disk is being re-evaluated.

2. Questions were asked about the clinical trials, including the number of neutropenic patients were in the clinical trials, the number of surgical debridements were performed in cSSSI trial, and the number of polymicrobial infections? The sponsor replied that no known neutropenic patients were enrolled, that there were no differences in the arms of the trial regarding debridements, and only a very small percentage of infections were polymicrobial.

3. A spirited discussion ensued around the wording proposed by the ad hoc WG concerning treatment of neutropenic patients. Part of the concerns centered on potential off-label use.

    a. There were concerns that this is setting a precedent that CLSI may not want to include in the books. Discussion about the neutropenic mouse model included the fact that many antibiotics perform less effectively in neutropenic mice compared to immunocompetent mice.
    b. It was noted that all drugs have some limitation, but these are comments that physicians should know from the package insert and should not be relegated to the clinical micro lab.
    c. The sponsor indicated that the drug is not indicated for neutropenic patients.
    d. The issue of a level playing field was raised about whether retroactively CLSI should add comments that are mentioned as warnings in drug labels.
    e. John Rex referred to M100, and noted that there are a few added comments that refer to issues that a micro lab should have within their purview, not something that is beyond their expertise. He advises not including the footnote.

4. A question was raised about the omission of *E. faecium* from the pathogen list. The sponsor indicated there is no indication for this, and there are no plans to obtain specific VRE data.

5. Footnotes to Tables 1A/1B and Table 2 were discussed.

- **WG Motion:** A motion was made and seconded to accept the FDA breakpoints. The motion was passed with a vote of Yes= 12; No = 0; Abstain = 2.

  Subcommittee Vote to accept the FDA breakpoints for Tedizolid: **Approved 9-0; 1 abstain, 1 absent**.

- **WG Motion:** A motion was made and seconded that no comment concerning neutropenia be included in the Table. The motion was passed with a vote of Yes = 9; No = 3; Abstain = 2

  Subcommittee agreed – no comment concerning neutropenia be included in the Table.

- **WG Motion:** A motion was made and seconded that footnotes describing the spectrum of organisms should be placed in Tables 1 and 2 (eg, For reporting against *S. aureus* only, including MRSA). The motion was passed with a vote of Yes = 13; No =0; Abstain = 1

  Subcommittee Vote to add footnotes describing the spectrum of organisms should be placed in Tables 1 and 2: **Approved 10-0; 1 absent**.

- A discussion of Test Report Groups resulted in a decision that Table 1 placement should be put on hold until Text and Tables clarifies the meaning of Group B Test and Report placement.

  - Group B Test and Report placement was clarified during the Subcommittee plenary session (see Report of Text and Table WG item #1) and the Subcommittee voted to approve Table 1 placement as suggested by the sponsor as follows:

    - For *Staphylococcus* spp. tedizolid is placed in Group B in same box with linezolid
    - For *Enterococcus* spp. tedizolid is placed in Group B in same box with linezolid
    - For *Streptococcus* spp. β-hemolytic group and *Streptococcus* spp. (viridans Group) tedizolid is placed in Group C in same box with linezolid

Subcommittee Vote: Approved 10-0; 1 absent

2) Report from Joint CLSI/EUCAST Polymyxin WG (See Briefing document 6.5.0)

Presenter: John Turnidge

The intention is to obtain a consensus testing method for polymyxins and a breakpoint for colistin between CLSI and EUCAST for *Pseudomonas aeruginosa* and *Acinetobacter* spp. Note that any decisions from CLSI will be presented to EUCAST later this month as a draft.

Recommendations for testing polymyxins:

1. Reference testing is the ISO-standard broth microdilution method, using
   a. cation-adjusted Mueller-Hinton Broth, with
   b. no additives in any part of the testing process (in particular, no polysorbate-80 or other surfactants);
   c. trays must be made of plain polystyrene and not otherwise treated before use, and
   d. sulfate salts of polymyxins must be used (in particular, the methanesulfonate derivative of colistin must not be used).

2. Disk diffusion and gradient diffusion testing require further studies to improve or confirm their correlation with reference method testing.

PK/PD in mice and humans

Mouse infection models:

- In a murine lung infection model, colistin is ineffective even for a stasis dose (*Pseudomonas* and *Acinetobacter*.) We don't know the target $fAUC_{24}$/MIC for Enterobacteriaceae.

- Target values of fAUC/MIC were much higher in the murine lung infection model than in the thigh infection model. In the case of the lung infection model with *A. baumannii*, it was only possible to determine target values for one of three strains; for the other two strains, stasis could not be achieved even at the highest tolerable doses.
- In both FDA and EMA modeling of approved doses, patients with normal renal function don't achieve high target attainment rates, even at colistin MICs of 0.5 (or 1) µg/mL.

Breakpoint proposal for colistin (Note that there is no recommendation for polymyxin B at this time.)

Breakpoint= 2 µg/L, only in patients with Cr Cl >75 mL/min at the highest possible doses (>300 mg/d) for *P. aeruginosa* and *Acinetobacter* spp.

This is identical to the current CLSI breakpoint.

Motion from the Joint WG: Don't change the CLSI MIC breakpoint.

Discussion points

1. Maybe we should lower the breakpoint to 1 µg/mL. We know that a number of patients don't respond if the breakpoint is 2 µg/mL but there are microbiological challenges in testing low colistin concentrations accurately.
2. One proposal was to set breakpoints dependent on renin functional status. We were reminded that we are moving to personalized/individualized medicine and this would be in line.
3. One proposal to call everything "Intermediate" and ask physicians to tailor the dosing to patients was met with resistance from physicians. It was noted that the drug is used extensively in patients who are complicated. Physicians already know that they usually need combination therapy, and that they will need to monitor the use of the drug during therapy.

WG Motions:

- **Motion:** Move the colistin breakpoint to 1 µg/mL.
  - The motion was not passed with a vote of Yes= 6; No = 6; Abstain = 2.
  - Dissenters:
    - We can reliably get an MIC; then personalize therapy in consultation with a PharmD or ID physician.
    - If you call all these strains resistant, then the drug virtually becomes nonexistent.
    - Colistin is used in combinations and may work synergistically with another drug.
  - Those in favor of the lower breakpoint:
    - Highest doses currently are being used, so the dose can't be increased. Toxicity needs to be considered.
    - We shouldn't assume that everyone will use this in combination.

- **WG Motion:** Establish the following colistin breakpoints: S = 0.5; I = 1-2; R ≥4 µg/mL for *Pseudomonas* and *Acinetobacter* spp.
    - Discussion centered on the lack of clinical data. Mike Satlin tried to find such data in the NY area. It is not easily attainable because so many patients receive combination therapy.
    - Question – how do you define I? You can't increase the dose. Do you suggest a pharmacy consult, or addition of a 2nd agent?

The motion was passed by the WG with a vote of Yes= 11; No = 2; Abstain = 1.

- Dissenters
    - We don't have enough data. Remove the breakpoint altogether.
    - Concern was voiced about setting breakpoints in the absence of clinical data.
- Further discussion:
    - A similarity to amphotericin was noted. We don't know what is really S and what is really R. We are pushing the data beyond what we really know.

John Turnidge reminded the WG that any decision should be regarded as tentative. There is supposed to be international harmonization. EUCAST will decide on this in a few weeks. Follow-up will be by an email vote so that the breakpoint can be printed in January.

Subcommittee Motion and Vote: SC proposed a 'Resistant only' breakpoint of ≥ 4 µg/mL with a need to determine a way to report isolates for which the MIC is < 4µg/mL. This would apply to *Pseudomonas* and *Acinetobacter* only. **Approved 9-2.** No change will be made in M100 yet since this decision is incomplete and will be shared with EUCAST as they are reviewing this as well and the two groups will try to possibly come together with a decision.

2nd motion by the Subcommittee pertained to Table 2B-5 (Other Non-*Enterobacteriaceae*): remove colistin and polymyxin B if there are no data to support the breakpoints in this table – **Approved 9-2**.

3) Breakpoint Proposal from Azithromycin/Shigella Breakpoint Ad Hoc WG (See Briefing document 6.3.0)

Presenter – John Turnidge

- Azithromycin is still used extensively for GI disorders
- BMD MIC data from 3 independent labs (USA, Argentina, Canada) were presented. Some tailing was seen with *S. sonnei* with some strains.
- Zone diameter reading issues were seen with *S. sonnei* but not *S. flexneri*.

Proposals from the Ad Hoc WG

1. Establish ECVs for *S. flexneri* and *S. sonnei* because the data requirement for doing this are fulfilled:
    a. *S. flexneri* ECV = 8 µg/mL
    b. *S. sonnei* ECV = 16 µg/mL

A WG Motion was made and seconded from the WG supporting this proposal: The motion was passed with a vote of Yes= 12; No = 0; Abstain = 2.

2. Establish a zone diameter correlate ECV for the *S. flexneri* of ≥16mm. None can be safely established for *S. sonnei* at this time.

A WG Motion made and seconded from the WG supporting this: The motion was passed with a vote of Yes= 13; No = 0; Abstain = 1.

3. Consider publishing (in S100 or as a separate document, e.g. rationale document), ECVs for these two species, and the zone diameter ECV for *S. flexneri.* (**WG:** No Motion was made on this.)

Discussion

- Many/most labs just call these *Shigella* spp. No speciation is possible. How do laboratories deal with this?
- Geographical differences were noted that may contribute to the DD reading issues.
    - Difficult S. *sonnei* populations are from Canada, and are most likely a clonal strain. Data from Canada should be treated separately.
    - Testing panels were different for one of the three sites, perhaps leading to lab-to-lab variation.
    - Zone sizes were much smaller for *S. sonnei* in the Argentina study compared to other 2 labs.

Subcommittee Motion and Vote: The Subcommittee voted to approve the proposals of the WG (Disk correlates and MIC ECV's for *S. flexneri* and MIC EVCs for *S. sonnei*) to be placed in a separate ECV table following current Table 2A – **Approved 8-1; 2 absent**.

4) Ceftolozane-Tazobactam Breakpoint Presentation (See Briefing documents 6.2.0, 6.2.1, 6.2.2, 6.2.3)

Presenters: Judith Steenbergen; Obi Umeh; Paul Ambrose

The following breakpoints for ceftolozane-tazobactam were approved by the FDA:

	MIC (µg/ml)			Zone Diameter (mm)		
Microorganism	S	I	R	S	I	R
Enterobacteriaceae	≤2/4	4/4	≥8/4			
Pseudomonas aeruginosa	≤4/4	8/4	16/4	≥21	17-20	≤16

Streptococcus spp. Viridans Group	≤8/4	16/4	≥32/4			

The sponsor requested that CLSI accept the FDA-approved breakpoints.

Discussion:

- People don't speciate streptococci in the clinical micro lab.
- A question was raised about using a fixed concentration of tazobactam in the in vitro testing method compared to its clinical use (2:1). The sponsor referred to a number of historical studies showing the advantage of testing with a fixed inhibitor concentration.
- A question was raised about harmonization with the FDA and the lack of a proposed CLSI breakpoint for *B. fragilis*. The sponsor reminded the group that metronidazole was included with ceftolozane-tazobactam in the cIAI clinical trials. The discussion centered on the issue as to whether CLSI needed to have complete harmonization with FDA. The consensus was that not all breakpoints had to be published in CLSI documents to have harmonization.
- Additional data for the disk diffusion assay for Enterobacteriaceae will be presented to the FDA. Following the FDA decision, the sponsor will come back to CLSI.
- The *Streptococcus* PK/PD slide was reviewed. The breakpoint was proposed to be 8 µg/ml, but at that MIC, a 2 $\log_{10}$ kill corresponded to only 83.5% target attainment. The sponsor indicated a 1 $\log_{10}$ kill was used for all other species. In the case for *Streptococcus*, the most conservative PK/PD target was used for analysis.
- For the Enterobacteriaceae the PD target attainment was approximately 85% based on stasis (84% for 2 $\log_{10}$ kill). Paul Ambrose proposed that the target should be stasis for UTI and IAI. indications

The Ad Hoc Working Group composed of Karen Bush (Chairholder), Aryun (Eileen) Kim, Amy Mathers, and Sandy Richter reviewed the company data with the sponsor and participated in two telephone conferences discussing the company proposals.

The Ad hoc WG supported publication of breakpoints for ceftolozane-tazobactam and was willing to accept the breakpoints set by FDA.

- Include in Table 2A, *Enterobacteriaceae* - MIC: S ≤2/4, I 4/4, R ≥8/4 µg/mL; Disk: no disk breakpoints.
- Include in Table 2B-1, *Pseudomonas aeruginosa* - MIC: S ≤4/4, I 8/4, R ≥16/4 µg/mL; Disk: S ≥21, I 17-20, R ≤16
- Include in Table 2H-2 – *Streptococcus* spp. Viridans Group - MIC: S ≤8/4, I 16/4, R ≥32/4 µg/mL; Disk: no disk breakpoints.

A WG Motion was made and seconded from WG to accept these breakpoints.

- The motion was passed with a vote of Yes= 10; No = 1; Abstain = 3.
- Dissent: The reviewer was not convinced that PK/PD supports the breakpoint for *Enterobacteriaceae.*

Subcommittee Motion and Vote: The Subcommittee vote to approve the recommendation of the Breakpoint WG to publish the FDA breakpoints – **Approved 8-1; 1 abstain, 1 absent**.

The sponsor also requested the following placement of ceftolozane-tazobactam in Table 1 of Document CLSI M100:

- For *P. aeruginosa* it is recommended that ceftolozane-tazobactam be placed in Group A (Primary Test and Report) as ceftolozane-tazobactam is the most potent anti-pseudomonal β-lactam (Table 6).
- For the *Enterobacteriaceae* and the *Streptococcus* spp. (viridans Group), it is recommended that ceftolozane-tazobactam be placed in Group B.

After reviewing the company data, the ad hoc WG proposed placement of ceftolozane-tazobactam in Table 1 of M100-S26 as follows:

- *Enterobacteriaceae*: Group B in box with other β-lactam/β-lactamase inhibitor combinations.
- *Pseudomonas aeruginosa*: Group B in own box.
- *Streptococcus* spp. Viridans Group: Group C in own box

Discussion

- The WG needs to figure out the correct placement of all drugs currently listed for *Pseudomonas* before we discuss the placement of ceftolozane-tazobactam.
- It was noted that this combination shouldn't be in Group A because ceftolozane-tazobactam can't be routinely tested at this point.

A WG Motion was made and seconded that ceftolozane-tazobactam be placed in Table 1 as recommended by the Ad Hoc Working Group.

- The motion was passed with a vote of Yes= 10; No = 1; Abstain = 3.
    - Dissent – Fix the Table before recommending placement of new drugs.

Subcommittee Motion and Vote: The Subcommittee voted to accept the recommendation for Table 1 placement recommended by the Ad Hoc WG – **Approved 8-1; 2 absent**.

A WG Motion was made and seconded that there should be a new footnote to *Streptococcus* spp. reports that it covers only *Streptococcus anginosus, Streptococcus constellatus* and *Streptococcus salivarius.*

- The motion was NOT passed with a vote of Yes= 4; No = 7; Abstain = 2
    - Dissent – Labs don't know speciate streptococci.

VII. REPORT OF THE TEXT AND TABLES WORKING GROUP *(*Electronic Folder 9)

Co - Chairholder – Ms. Jana Swenson
Co - Chairholder – Ms. Maria Traczewski
Recording Secretary – Carey-Ann Burnham (absent)

Members Present: Dale Schwab, Peggy Kohner, Linda Mann, Janet Hindler, Tom Thomson, Dyan Luper, Nancy Watz

Members absent: Melissa Miller, Flavia Rossi

1. **Wording of Group B Test/Report Group**

   During discussions in the Breakpoint WG, it was pointed out that the definition of the Group B Test/Report Group was not clear. In the M100 Instructions for Use the definition includes the wording "may warrant primary testing":

   > **Group B** includes antimicrobial agents that may warrant primary testing, but they may be reported only selectively, such as when the organism is resistant to agents of the same antimicrobial class, as in Group A.

   In Tables 1, the heading is

   > **GROUP B**
   > **PRIMARY TEST**
   > **REPORT SELECTIVELY**

   giving the impression that the testing of agents in Group B is required.

   To fix this it was decided to add the word "OPTIONAL" to the heading, ie, "OPTIONAL PRIMARY TEST".

   No vote required—editorial revision only.

2. During review of M100, it was pointed out that Table 2 comments can sometimes be difficult to locate. To help with this it was decided to do two things, 1) bold the comment numbers, and 2) lighten the shading in the gray boxes.

   It was also decided that creating a new table with body-site specific information (ie, for urinary tract infections, etc.) to include in M100 Instructions for Use which would allow us to clean up Tables 2. Therefore it was decided that an ad hoc group be formed with Janet Hindler as lead, to do this.

   No vote required.

3. A request was made to T&T to add information on reading linezolid MICs to M100. The reason for this is that information on disk testing is included in M100 but not MIC testing. A new general comment was proposed which uses wording currently in M07 to be added to gram-positive tables 2C, 2D, 2G, 2H-1 and 2H-2 as follows:

   (2) For gram-positive cocci when testing chloramphenicol, clindamycin, erythromycin, linezolid, tedizolid and tetracycline by MIC, 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 M07 Figures 3 and 4). With trimethoprim and the sulfonamides, antagonists in the medium may allow some slight growth; therefore, read the end point at the concentration in which there is ≥ 80% reduction in growth as compared to the control (see M07 Figure 2).

Later at the plenary session tedizolid was added to the comment (shown above in red).

No vote required—editorial revision only.

4. A request to clarify recommendations for testing *Salmonella* and fluoroquinolones was considered by the working group. The subcommittee did approve in-concept having the *Salmonella*/fluoroquinolone piece pulled out on its own in the table with no changes to the nalidixic acid breakpoints or associated comment (**Approved 9-1; 1 absent**). A final revised version was not able to be completed during the meeting and will be circulated by email after the meeting.

5. WG reviewed several photographs for Carba-NP test and decided to use them for the next version of M100. One photograph included examples of Tube A next to tube B for all possible test results. A second photo will show all possible colors of tube B.

6. Revision of M02 and M07

Next published revision of M02 and M07 is scheduled for January 2018. In order to do this more efficiently, it was decided to create a small ad hoc group to meet between now and January 2016. This group would then present their suggested revisions to the T&T group in January 2016. The goal would be to have a near complete draft available in January 2017 and a final draft in the agenda book in June 2017.

7. Report of the Outreach Ad Hoc WG

Co - Chairholder – Ms. Janet Hindler
Co - Chairholder – Dr. Audry Schuetz

Members Present: Marcelo Galas, Romney Humphries, Beth Prouse, Nicole. E. Scangarella-Oman

Members Absent: Violeta J. Rekasius, Lars Westblade

Topic	Details	Followup
IQCP AST materials	**Automated AST System IQCP** final materials are posted on ASM and CLSI websites; DD to be posted on website soon. **Educational programs:** • Webinar #1 – September AST IQCP (IQCP members Linda Bruno and Susie Sharp) • Webinar #2 – November AST IQCP with emphasis on confirming results before reporting and turn around time. (Beth and Janet)	Janet check with CLSI for scheduling webinars All to contribute to "top 10" (webinar #2)

	Tracy will post materials link on DivC, check FB status and Twitter CLSI pages to reach out to labs which are not subscribers to DivC. Determine if there is mechanism to reach all 26,000 high complexity labs that are likely doing AST (e.g., through state PH Labs) CLSI to fix CLSI website link text to reflect "IQCP" (Janet informed IQCP WG) Links to posted IQCP materials: http://clinmicro.asm.org/index.php/lab-management/laboratory-management/445-iqcp-iqcp http://clsi.org/standards/micro/sub-ast/	Violet? to check on reaching high complexity labs **Timeline**: ASAP for webinar dates and fixing CLSI website
CRE Educational Materials	**CRE** Develop: 1) Powerpoint presentation with explanation like ppt presentations on CDC websites Focus is on testing and reporting of CREs. Will not pursue issues of surveillance and MDRO screening other than CRE. Get feedback from Lars (will contact others), April, Stella, Fred; then Janet/Romney to finalize) 2) Frequently asked questions (Romney and Lars) 3) Case study (Audrey) 4) List of resources for labs needing help with CRE?	**Timeline**: Complete by mid August
AST SC Workshops	**Educational workshop** proposals for January and June 2016 **Ideas:** • Newer methods of resistance detection (e.g., molecular and novel biological growth methods) • LDT vs RUO vs surrogate	Nicole/Romney collect suggestions from all and confirm topic at next call **Timeline**: July call (topic)
CLSI AST SC Webpage (meeting materials)	**CLSI AST SC webpage** containing material from biannual meetings http://clsi.org/standards/micro/microbiology-files/ Determine how best to organize and what is possible within CLSI IT structure.	Violet and Lars **Timeline**: TBD (neither Lars or Violet at June 15 WG meeting)
Resources available	**"Discovery" to determine resources available for AST** (i.e., resources available for educational links concerning antimicrobials and education concerning antimicrobial testing) • Considered addition of IDSA (Tracy will send link) and CMS resources to add to the table Beth will reformat materials in tabular form by topic. This will be provided as a link in our newsletter.	Beth and Nicole **Timeline**: Complete by July call
Information Desired	• **"Discovery" to determine information needed** by constituents to help select content for educational materials.	Marcelo and Lars **Timeline**:

	On hold since we have several projects to work on now.	
Newsletter	Develop a periodic **newsletter** to inform constituents of ORWG activities. Pattern after ASM CMMC Newsletter…see link here http://clinmicro.asm.org/images/archive/CMMC_Newsltr_4_21_15.pdf • ORWG will develop content and CLSI will format using one of CLSI newsletter formats • Twice per year with updates as needed. Glen Fine discussed the possibility of linking ORWG educational efforts with Veterinary and Antifungal groups' materials – Audrey will reach out to antifungal group. • Add Q&A on verification of AST? (Mike Loefholtz agreed to help)	**Group** **Timeline:** Fall 2015
Case Studies	Will do CRE Case to compliment CRE educational program	See above
Future ORWG meetings	CLSI will send out a Doodle request for July meeting.	Patrick/Tracy

VIII. USCAST/NAC INFORMATIONAL DISCUSSION

Jean Patel provided a description of the USCAST process based upon email exchanges with Ron Jones and Paul Ambrose. USCAST was invited to present this information to the Subcommittee but declined. The following process was presented:

USCAST Process:

- USCAST will develop documents that contain breakpoint proposals and data to support the proposal.
- The documents will be available on the USCAST website for 30 days.
- The documents are copyrighted
- USCAST will solicit comments on the first draft of the document
- The comments are used by USCAST to revise the document. The comments are not made public.
- The revised document is given to EUCAST for decision making
- A final document will be posted on the USCAST website after EUCAST has made a decision.

USCAST members present were asked to confirm or correct this. Paul Ambrose confirmed this as correct.

IX. REPORT OF THE QUALITY CONTROL WORKING GROUP (Electronic Folder 7)

Co-Chairholder – Dr. Steven Brown
Co-Chairholder – Ms. Sharon Cullen

Members Present: Patti Conville, Bob Flamm, Stephen Hawser, Janet Hindler, Denise Holliday, Michael Huband, Ross Mulder, Susan Munro, Jim Ross, Mary York
Members Absent: Erika Matuschek

1. **M23 Tier 2 Quality Control Study Challenges:**

Methods Working Group is addressing proposed modifications to standard methods with QCWG inputs. M23 indicates that standard reference methods should be used. Sponsors are reminded that modifications can be made but should be justified (eg, standard method is not reproducible or doesn't correlate with *in vivo* results).

2. **M23 Tier 2 QC Studies: Preferred QC organism for avibactam vs other β lactamase inhibitor combinations for Nonfastidious Organisms**

Sponsors are reminded that *K. pneumoniae* ATCC® 700603 must be used with avibactam combination drugs for adequate quality control. Either *E. coli* ATCC® 35218 or *K. pneumoniae* ATCC® 700603 can be used for tazobactam combinations and other β-lactamase inhibitor combinations. If ranges existed for *K. pneumoniae* ATCC® 700603 with all β-lactamase inhibitor combinations, we could potentially eliminate the need to test *E. coli* ATCC® 35218 routinely in the future.

QC ranges currently exist for *K. pneumoniae* ATCC® 700603 with avibactam and β-lactamase inhibitor combinations for all antimicrobial agents listed on current QC tables in M100-S26 draft for MICs but not for disk diffusion. QC Study sponsors/coordinators are requested to include these Tier 2 Studies for disk diffusion so that we can establish QC ranges for *K. pneumoniae* ATCC® 700603 and allow users to reduce the number of QC strains tested routinely.

- Amoxicillin-clavulanate, Ampicillin-sulbactam, Piperacillin-tazobactam, Ticarcillin-clavulante,

3. **Availability of 2 disk manufacturers for M23 Tier 2 Studies.**

Concerns were discussed that it is not always possible to have two disk manufacturers in time for Tier 2 QC Studies. Tier 2 guidelines were established to provide reasonable confidence with reasonable cost

- Disks: Use of 2 different manufacturers (if possible),
- MIC: Only one manufacturer required for panels

Discussion indicated that there have been examples where performance is different with different manufacturers but this was infrequent or rare. Tier 3 Guidelines exists to evaluate additional data (eg, more labs, bigger sample size, more manufacturers) and could be used to confirm the original range or adjust if needed.
Motion passed to encourage pursuit of 2 disk manufacturers. If not available, accept data from a single disk manufacturer and add footnote "Range established with single manufacturer of disks." (11 approved; 0 opposed; 2 absent).

This footnote could be removed when data from 2nd disk manufacturer is presented and accepted. Note: We will need to define a process for type/quantity of data needed.

4. IQCP:

Members: Susan Munro, Chair; Linda Bruno, ACL Labs, Recording Secretary; Mary Arndt, Beckman Coulter; Janet Hindler, UCLA; Susie Sharp, Kaiser; Maria Traczewski, Clinical Microbiology Institute; Barbara Robinson, ASM representative; Kathleen Todd, CMS representative; Penny Keller, CMS representative.

This Ad Hoc group is working on a collaborative project with ASM and CAP. The goal is to provide guidance to clinical microbiology laboratories to support lab implementation by CMS deadline of Jan. 2016. Documents have been created to explain the new CMS requirements for an Individualized Quality Control Plan (IQCP), as well as how to create and implement an IQCP using three components Risk assessment, QC Plan, and QA.

The following materials have been completed and are posted on the ASM Clinical Microbiology portal at https://clinmicro.asm.org/index.php/lab-management/laboratory-management/445-iqcp and CLSI website at http://clsi.org/standards/micro/sub-ast

- Introduction
- Q & A
- IQCP for Commercial MIC system (PowerPoint)
- Example of IQCP for Commercial MIC system

5. Tier 3 QC:

As part of the routine Tier 3 monitoring of QC performance, out of range results (or data at the edge of the current range) have been reported for the following. Data is requested from members of the AST Subcommittee and QC study sponsors/coordinators in order to assess whether or not the current ranges need to be revised. Routine disk diffusion data is acceptable; data from frozen reference is needed for MIC (data from commercial MIC devices cannot be used). The original M23 Tier 2 data is also needed from pharmaceutical companies/QC study coordinators. A request will also be sent to ASM Division C. Submit data to Sharon Cullen and notify her if issues are seen with other agents.

a. Disk Diffusion

- Cefepime and *P. aeruginosa* ATCC® 27853: Out high, Lab variability
- Cefixime and *E. coli* ATCC® 25922: Out low
- Meropenem and *E. coli* ATCC® 25922: Out high (5%)

b. MIC

- Cefuroxime and *S. pneumoniae* ATCC® 49619: Mode at low end of range (0.25) with one lab

6. **Troubleshooting Guide:**

   Updates are needed for both Disk and MIC Troubleshooting Guides. We should incorporate information from M2 and M7, obtain feedback from AST Subcommittee participants on other improvements and incorporate recommendations from Ad Hoc Group for Broth Microdilution. The Troubleshooting Guide provides valuable information to many stakeholders and is a valuable source of information for users to create IQCP. The proposed timeline is to have a draft for review/discussion in January 2016 and follow up on questions and get final approval in June 2016. Volunteers requested to review and propose updates.

   - Disk: Denise Holiday and Erika Matuschek
   - MIC: Patti Conville. Need additional volunteer

7. **QC Range Proposals (see Appendix B at the end of these minutes for all QC reviewed and approved)**

X. AGENDA SUBMISSIONS FOR 10-12 JANUARY 2016 MEETING IN TEMPE ARIZONA

Materials for the January meeting will be distributed to the subcommittee prior to the meeting. The meeting rooms will be equipped with power strips for those who prefer to view the material on their computer instead of printing the material. Please note there will not be internet access in the meeting rooms.

To meet the schedule to have materials available for review a few weeks prior to the meeting, submission due dates and requirements must be met. In order to present at the 10-12 January 2016 meeting please:

1) Submit agenda materials electronically as a PDF file **on or before Monday, 7 December 2015.**

Please Note: For QC submissions based on M23 Tier 2 Studies please make sure to include:

- **Information for the solvent and diluent to include in Table 6**
- **Antimicrobial class and subclass, antimicrobial agent abbreviation, and route of administration for inclusion in Glossary I and II.**

2) E-mail proposed agenda topics to Jean B. Patel, PhD, D(ABMM) (vzp4@cdc.gov) and Tracy Dooley (tdooley@clsi.org) for review.

XI. ADJOURNMENT – The meeting adjourned at 11:05 a.m. on Tuesday, 15 June 2015.

Respectfully submitted,

Tracy A. Dooley, BS, MLT (ASCP),
Senior Standards Project Manager

Appendix A. Addition to Table 2C for *S. pseudintermedius* (new information shown in red):

Table 2C. (Continued)

Test/Report Group	Antimicrobial Agent	Disk Content	Zone Diameter Interpretive Criteria (nearest whole mm)			MIC Interpretive Criteria (µg/mL)			Comments
			S	I	R	S	I	R	
PENICILLINASE-STABLE PENICILLINS (Continued)									
A	Oxacillin For *S. aureus* and *S. lugdunensis.*		–	–	–	≤ 2 (oxacillin)	–	≥ 4 (oxacillin)	For use with *S. aureus* and S. *lugdunensis*. **(11)** Oxacillin disk testing is not reliable. See cefoxitin and comment (4) for reporting oxacillin when testing cefoxitin as a surrogate agent.
		30 µg cefoxitin (surrogate test for oxacillin)	≥ 22	–	≤21	≤ 4 (cefoxitin)	–	≥ 8 (cefoxitin)	**(12)** Cefoxitin is tested as a surrogate for oxacillin; report oxacillin susceptible or resistant based on the cefoxitin result. See comments (4), (7), and (10).
A	Oxacillin For CoNS except *S. lugdunensis.*	–	–	–	–	≤0.25 (oxacillin)	–	≥0.5 (oxacillin)	For use with CoNS except *S. lugdunensis.* **(13)** Oxacillin MIC interpretive criteria may overcall resistance for some CoNS, because some non–*S. epidermidis* strains for which the oxacillin MICs are 0.5–2 µg/mL lack *mecA*. For serious infections with CoNS other than *S. epidermidis,* testing for *mecA* or for PBP 2a or with cefoxitin disk diffusion may be appropriate for strains for which the oxacillin MICs are 0.5–2 µg/mL.
		30 µg cefoxitin (surrogate test for oxacillin)	≥25	–	≤24	–	–	–	See comments (4), (7), (10), and (12).
A	**Oxacillin** **For *S. pseudintermedius***	**1 µg oxacillin**	**≥18**	**–**	**≤17**	**≤0.25**	**–**	**≥0.5**	**(XX) Neither cefoxitin MIC nor cefoxitin disk tests are reliable for detecting *mecA*-mediated resistance in *S. pseudintermedius*.**

Appendix B. QC Ranges Reviewed:

All QC ranges shown in Appendix B were approved by the Subcommittee (Approved 9-0:2 absent)

Drug Name:	**Aztreonam-Avibactam**			
Table 6 information:	**Solvent: NA (used commercial disks)**	**Diluent: NA (used commercial disks)**		
Table 6C information:	**Combination Tested:30/20 µg disks**	**Preparation: N/A**		**Example:**
Glossary information:	**Class:monobactam-β-lactamase inhibitor**	**Subclass: N/A**	**Agent Abbreviation: TBD**	**Route of Administration: TBD**

QC Strain (ATCC®)	QC Range Approved mm or dil	WG Vote: Y/N/A/ NP	% in Range	Mode/ Median	# mm or dilutions	Shoulder %	Footnote to add with drug/range	Variability/Comments
E. coli **ATCC® 25922**	**32-38**	**9/0/2/2**	**97.5**	**35**	**7**	**NA**		**Proposed 32-38 (97.5%, 7mm) or 31-38 (99.4%, 8mm)** **RF: 30-38mm (9mm)**
P. aeruginosa **ATCC® 27853**	**24-30**	**9/0/2/2**	**100**	**27**	**7**	**NA**		**Original proposal 25-29 (98.5%, 5mm). Concern 5mm range too narrow** **RF: 21-32 (12mm)**
E. coli ATCC® 35218	**31-38**	**9/0/2/2**	**98.5**	**35**	**8**	**NA**		**Original proposal 32-38 (96.5%, 7mm)** **Lab median 33-37.** **Media B 6% of results @ 31** **RF: 31-39 (9mm)**
K. pneumoniae **ATCC® 700603**	**26-32**	**9/0/2/2**	**99.2**	**29**	**7**	**NA**	**Add footnote d from Table 4A and f from 5A**	**RF: 26-32 (7mm)**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study conducted by CMI for AstraZeneca Pharmaceuticals (Report ATM-AVI-M2-026) – No significant media or disk variability observed. Some lab to lab variability.

Proposed and approved by QCWG by email vote (8 for, none against, 6 no response when minutes were finalized) after the AST Subcommittee meeting (not discussed during the AST meeting) to add footnote currently used for other avibactam combinations on the MIC and Disk QC tables. Also recommended revising the statement to remove list of drugs to avoid need to update as new compound are added.

Appendix B Continued.

Drug Name:	**Aztreonam**			
Table 6 information:	**Solvent: No change**	**Diluent: No change**		
Table 6C information:	**Combination Tested: NA**	**Preparation: No change**		**Example: NA**
Glossary information:	**Class: Monobactam (No change)**	**Subclass: None**	**Agent Abbreviation: ATM, AXT, Axt, AT, AZM (No change)**	**Route of Administration: No change**

QC Strain (ATCC®)	QC Range Approved mm or dil	WG Vote: Y/N/A/NP	% in Range	Mode/ Median	# mm or dilutions	Shoulder %	Footnote to add with drug/range	Variability/Comments
E. coli **ATCC® 25922**	**28-36**	**Current**	**99.6%**	**33**	**9**			**Currently range 28-36 (99.6% for this study, 9mm). Gavin stats 30-36 (7mm) RF: NA**
P. aeruginosa **ATCC® 27853**	**23-29**	**Current**	**100%**	**26**	**9**			**Currently range 23-29 (100% for this study, 9mm). Gavin stats 24-28 (5mm) RF: NA**
E. coli **ATCC® 35218**	**31-38**	**10-0-1-2**	**99.4%**	**34**	**8**			**Original proposal 31-37 (97.7%, 7mm) or 31-38 (99.4%, 8mm) RF: 30-38mm (9mm) Matches range approved for Aztreonam-avibactam**
K. pneumoniae **ATCC® 700603**	**10-16**	**10-0-1-2**	**99.0**	**13**	**7**			**Proposed 10-16 (99.0%, 7mm) or 11-15 (97.5%, 5mm) RF: 11-15mm (5mm)**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study conducted by CMI for AstraZeneca Pharmaceuticals
No significant variability observed.

Appendix B. Continued

Drug Name:	**Cadazolid**			
Table 6 information:	**Solvent:** **DMSO**	**Diluent:** **Water or Broth**		
Table 6C information if applicable:	**Combination Tested: NA**	**Preparation: N/A**		**Example:**
Glossary information:	**Class: Quinolonyl oxazolidinone**	**Subclass: NA**	**Agent Abbreviation: CDZ**	**Route of Administration: Oral**

QC Strain (ATCC)	QC Range Approved mm or dil	WG Vote: Y/N/A/NP	% in Range	Mode/ Median	# mm or dilutions	Shoulder %	Footnote to add with drug/range	Variability/Comments
C. difficile **ATCC® 700057**	**0.12-0.5 Agar**	**10/0/1/2**	**100**	**0.25**	**3**	**<10%**		**Some media variability.**
C. difficile **ATCC® 700057**	**0.06-0.25 Broth**	**10/0/1/2**	**97.9**	**0.12**	**3**	**<25%**		**Lab variability observed. RF: 0.03-0.25**
E. faecalis **ATCC® 29212**	**0.06-0.25 Broth**	**10/0/1/2**	**99.3**	**0.12**	**3**	**<20%**		
S. aureus **ATCC® 29213**	**0.06-0.5 Broth**	**10/0/1/2**	**100**	**0.12**	**4**	**59.3% @0.25**		**Media lot 3 mode 0.25 RF: 0.06-0.5**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study conducted by IHMA Europe for Actelion.
C. diff agar: Lab D omitted due to low inoculum counts (mode was 0.12 with 7/30 @ 0.06)
C. diff broth. Lab E omitted due to out of range high control drug results.
Note: No special reading instructions are required. Trailing reported with linezolid or tedizolid has not been observed with Cadazolid.

Appendix B. Continued				
Drug Name:	**Levonadifloxacin (WCK 771)**			
Table 6 information:	**Solvent: 27.5 mg/mL solution of L-arginine in water. *Delete 27.5% from agenda materials*.**	**Diluent: Water**		
Table 6C information:	**Combination Tested: NA**	**Preparation: N/A**		**Example:**
Glossary information:	**Class: Quinolone**	**Subclass: Benzoquinolizine**	**Agent Abbreviation: LND**	**Route of Administration: IV**

QC Strain (ATCC)	QC Range Approved mm or dil	WG Vote: Y/N/A/NP	% in Range	Mode/ Median	# mm or dilutions	Shoulder %	Footnote to add with drug/range	Variability/Comments
S. aureus **ATCC®29213**	**0.008-0.03**	**11/0/1/1**	**100**	**0.015**	**3**	**34%**		**Media B 0.008 mode**
E. coli **ATCC®25922**	**0.03-0.25**	**11/0/1/1**	**100**	**0.06**	**4**	**71% @ 0.12**		**Media A mode 0.12 Proposed 0.03-0.25 (100%, 4dil) or 0.03-0.12 (98.1%, 3dil)**
P. aeruginosa **ATCC®27853**	**0.5-4**	**11/0/1/1**	**100**	**2**	**4**	**60.5% @1**		**Original proposal 0.05-8 (100%, 5 dil). Large range unacceptable. Media B mode@1. Lab variability Proposed 0.5-8 (100%, 5dil). RF 0.5-4**
S. pneumoniae **ATCC®49619**	**0.12-0.5**	**11/0/1/1**	**100**	**0.25**	**3**			**No significant variability observed (93.7% of results 0.25). RF: 0.12-0.25**
H. influenzae **ATCC®49247**	**0.008-0.06**	**11/0/1/1**	**100%**	**0.015**	**4**	**57.8% at 0.03**		**Media A mode 0.015, Media B&C 0.015-0.3). Lab variability Proposed 0.008-0.06 (100%, 4dil) or 0.008-0.03 (99.6%, 3dil) RF 0.008-0.03**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study conducted by IHMA for Wockhardt Bio AG. RF inputs provided at meeting but not in agenda materials

Appendix B. Continued

Drug Name:	**Levonadifloxacin (WCK 771)**			
Table 6 information:	**Solvent: 27.5 mg/mL solution of L-arginine in water. Delete 27.5% from agenda materials.**	**Diluent: Water**		
Table 6C information:	**Combination Tested: N/A**	**Preparation: N/A**	**Example:**	
Glossary information:	**Class: Quinolone**	**Subclass: Benzoquinolizine**	**Agent Abbreviation: LND**	**Route of Administration: IV**

QC Strain (ATCC)	QC Range Approved mm or dil	WG Vote: Y/N/A/NP	% in Range	Mode/ Median	# mm or dilutions	Shoulder %	Footnote to add with drug/range	Variability/Comments
S. aureus **ATCC®25923**	**32-39**	**11/0/1/1**	**97.8%**	**36**	**8**		**Range established with one disk manufacturer.**	**Lab D had 5/60 from 29-31mm. Media A had 4/18 from 29-31mm. Media variability also with levofloxacin control. Proposed 32-39 (97.8%, 8mm) or 33-39 (94.2%, 7mm) RF 32-39**
E. coli **ATCC®25922**	**27-33**	**11/0/1/1**	**98.5**	**30**	**7**		**Same as above.**	**RF 27-33**
P. aeruginosa **ATCC®27853**	**17-23**	**9/2/1/1**	**99.8**	**20**	**7**		**Same as above.**	**Original proposal 18-22 (97.7%, 5mm). Concerns with small zone RF 17-23**
S. pneumoniae **ATCC®49619**	**24-31**	**9/2/1/1**	**99.3**	**27**	**8**		**Same as above.**	**Media medians 26, 27, 28 Some lab variability. Concern about inoculum with small zones (consider for troubleshooting). Proposed 24-31 (99.3%, 8mm) or Gavin stat 24-30 (96.1%, 7mm) RF 24-31**
H. influenzae **49247**	**33-41**	**11/0/1/1**	**96.3**	**37**	**9**		**Same as above.**	**Media A median @ 36, B @37, C @ 38. Lab medians from 34-40 RF 33-42**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study conducted by IHMA for Wockhardt Bio AG. RF inputs provided at meeting but not in agenda materials

Appendix B. Continued

Drug Name:	**WCK 4783**			
Table 6 information:	**Solvent: ½ volume of water, then glacial acetic acid drop wise to dissolve (acetic acid not to exceed 2.5 µl/mL)**	**Diluent: Water**		
Table 6C information if applicable:	**Combination Tested: N/A**	**Preparation: N/A**		**Example:**
Glossary information:	**Class: Macrolide**	**Subclass: Ketolide**	**Agent Abbreviation: ZWK**	**Route of Administration: Oral**

QC Strain (ATCC)	QC Range Approved mm or dil	WG Vote: Y/N/A/NP	% in Range	Mode/ Median	# mm or dilutions	Shoulder %	Footnote to add with drug/range	Variability/Comments
***S. aureus* 29213**	**0.06 – 0.25**	**8/3/1/1**	**100**	**0.12**	**3**	**13%@0.06**		**RF 0.06-0.25**
***E. faecalis* 29212**	**0.015 – 0.12**	**7/4/1/1**	**100**	**0.03**	**4**	**49.4% @ 0.06**		**Proposed 0.015 – 0.06 (98.5%, 3 dil) or 0.015 – 0.12 (100% 4 dil) Media C mode 0.06. No results @0.015. RF 0.015-0.06 Initial vote for 0.015-0.06 8/3/1/1. Final vote for 0.015-0.12.**
***S. pneumoniae* 49619**	**0.008 –0.03**	**8/3/1/1**	**100**	**0.015**	**3**	**<5%**		**RF 0.015-0.015**
***H. influenzae* 49247**	**2 – 8**	**8/3/1/1**	**100**	**4**	**3**	**<10%**	**Range established with single manufacturer of disks.**	**RF 2-4**
***S. aureus* 25923**	**25 – 31**	**11/0/1/1**	**97.0**	**28**	**7**	**N/A**	**Same as above**	**Lab median ranged from 26-30. RF 24-32**
***S. pneumoniae* 49619**	**25 – 31**	**11/0/1/1**	**98.7**	**28**	**7**	**N/A**	**Same as above**	**RF 25-31**
***H. influenzae* 49247**	**16-20**	**11/0/1/1**	**99.4**	**18**	**5**	**N/A**	**Same as above**	**Some discussion about narrow range. Adjust with Tier 3 later if needed. RF 24-20**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study conducted by IHMA for Wockhardt Bio AG. RF inputs provided at meeting but not in agenda materials

Drug Name:	**Delafloxacin**			
Table 6 information:	**Solvent: 1/2 volume of water, then 0.1 mol/L NaOH dropwise to dissolve (no change)**	**Diluent: Water (no change)**		
Table 6C information if applicable:	**Combination Tested: N/A**	**Preparation: N/A**		**Example:**
Glossary information:	**Class: quinolone (no change)**	**Subclass: fluoroquinolone (no change)**	**Agent Abbreviation: DLX (no change)**	**Route of Administration: IV/PO (no change)**

QC Strain (ATCC)	QC Range Approved mm or dil	WG Vote: Y/N/A/NP	% in Range	Mode/ Median	# mm or dilutions	Shoulder %	Footnote to add with drug/range	Variability/Comments
***S. pneumoniae* 49619**	**28-36**	**12/0/0/1**	**99.6**	**31.5**	**9**	**NA**	**Range established with single manufacturer of disks.**	**Gavin: 28-34mm (96.3%, 7mm) RF: 27-36mm (99.6%, 9mm) Lab median ranged from 30-34**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study presented in Jan 2015 had insufficient lab data after removal on 2 labs (one due to control drug, one statistical outlier lab). 2 labs (one due to control drug, one statistical outlier lab). Proposed range was 29-36 with 99.7% included and median 32mm.

New 9 lab study presented by Micromyx for Melinta Therapeutics.
Results from Lab 4 removed (larger zones, outlier for mean and mode). Lab 4 control drug results were within range.
Note: Lab 4 was also removed from Jan 2015 data. Cause for larger zones unknown.

Appendix B. Continued

Drug Name:	**Eravacycline (TP-434)**			
Table 6 information:	**Solvent: Water**	**Diluent: Water**		
Table 6C information if applicable:	**Combination Tested: N/A**	**Preparation:** N/A		**Example:**
Glossary information:	**Class: Tetracycline**	**Subclass: fluorocycline**	**Agent Abbreviation: ERV**	**Route of Administration: IV and oral**

QC Strain (ATCC)	QC Range Approved mm or dil	WG Vote: Y/N/A/NP	% in Range	Mode/ Median	# mm or dilutions	Shoulder %	Footnote to add with drug/range	Variability/Comments
C. difficile **700057 broth**	**0.015-0.06**	**11/0/1/1**	**99.6**	**0.03**	**3**	**<25%**	**Broth microdilution**	
B. fragilis **25285 broth**	**0.015-0.12**	**11/0/1/1**	**100**	**0.06**	**4**	**58.9% @ 0.03**	**Broth microdilution**	**3 Labs with mode @ 0.03. RF: 0.03-0.12 (100%, 3 dil)**
B. thetaiotaomicron **29741 broth**	**0.06-0.25**	**11/0/1/1**	**99.3**	**0.12**	**3**	**22% @0.06**	**Broth microdilution**	**Lab F mode at 0.06 RF: 0.06-0.25**
E. lentum **43055 broth**	**No range**	**No vote**						**Mode across 3 dilutions 0.008-0.03. Media no significant variability. Lab mode 0.008 to 0.03. RF: 0.004-0.06 (5 dil)**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study conducted by IHMA Europe for Teraphase.
E. lenta gives variable results with some antimicrobial agents. It grows well in Columbia but not Brucella broth. Referred to Anaerobe working group for clarification on when/if E. lenta should be tested in Tier 2 QC Studies.

Ranges approved previously for Agar dilution: C. diff 0.06-0.25, B frag 0.06-0.25, B. theta 0.12-1, E. lentum no range.

Appendix B. Continued

Drug Name:	**Secnidazole**			
Table 6 information:	**Solvent: DMSO**	**Diluent: Water**		
Table 6C information if applicable:	**Combination Tested: N/A**	**Preparation: N/A**		**Example:**
Glossary information:	**Class: Nitroimidazoles**	**Subclass: N/A**	**Agent Abbreviation: SEC**	**Route of Administration: PO**

QC Strain (ATCC)	QC Range Approved mm or dil	WG Vote: Y/N/A/NP	% in Range	Mode/ Median	# mm or dilutions	Shoulder %	Footnote to add with drug/range	Variability/Comments
***B. fragilis* 25285 (Agar)**	**0.25-1**	**12/0/0/1**	**100**	**0.5**	**3**	**50.6% @ 0.25**		**Media A bimodal 0.25-0.5 Lab 4 and 8 mode at 0.25**
***B. thetaiotaomicron* 29741 (Agar)**	**0.5-2**	**12/0/0/1**	**100**	**1**	**3**	**34.7% @ 2**		**Lab 1 & 9 mode at 2. No significant media variability.**
***C. difficile* 700057 (Agar)**	**0.06-0.5**	**12/0/0/1**	**100**	**0.12**	**4**	**72.2% @ 0.25**		**Lab 1, 6 & 9 mode at 0.25. Removed Lab 3 and 4**
***E. lentum* 43055 (Agar)**	**0.25-2**	**12/0/0/1**	**100**	**1**	**4**	**68.3% @ 0.5**		**Lab 6 & 8 mode at 0.5. Media C mode at 0.5**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study presented by Micromyx for Symbiomix Therapeutics.
Lab 3 was a statistical outlier for B. fragilis 25285 (mode @ 4), B. thetaiotaomicron 29741 (mode 4), and C. difficile 700057 (mode 2). Lab 4 was out of QC for clindamycin for C. difficile ATCC 700057 (mode 0.25, range 2-8). These data were excluded from the final analysis

RF inputs provided at meeting but not in agenda materials and supported proposed ranges.

Drug Name:	**BAL30072**			
Table 6 information:	**Solvent: DMSO**	**Diluent: DMSO**		
Table 6C information if applicable:	**Combination Tested: N/A**	**Preparation: Stock solution may be diluted with water or broth for preparation of working solution.**		**Example: Stock 3200 mg/ml prepared with DMSO. Working concentration of 320 mg/ml prepared by diluting stock 1:10 with water or broth.**
Glossary information:	**Class: monoclyclic β-lactam**	**Subclass: sulfactams**	**Agent Abbreviation: TBD**	**Route of Administration: TBD**

QC Strain (ATCC)	QC Range Approved mm or dil	WG Vote: Y/N/A/NP	% in Range	Mode/ Median	# mm or dilutions	Shoulder %	Footnote to add with drug/range	Variability/Comments
E. coli **25922**	**0.06-0.25**	**9/2/1/1**	**96.3%**	**0.12**	**3**	**48.6% @0.06, 59.5% @0.25**		**Note incorrect entry on page 8 with proposal for 0.03-0.25 Some media variability. Lab mode 0.06 – 0.25 Proposed 0.06-0.25 (96.3%, 3 dil) or 0.06-0.5 (99.6% 4 dil) RF: 0.06-0.25 (100%, 3 dil) Counter 0.06-0.5 was not approved with vote 3/8/1/1**
P. aeruginosa **27853**	**1-8**	**10/0/2/1**	**96.7%**	**2**	**4**	**67.5% @1, 91.5% @4**		**Media mode ranged from 1-4. 5 Labs mode @ 4, 3 mode @ 2 RF: 0.5-8 (98.8%, 5 dil) Concern about 2 dil shift with media. Lot 1 has been used in most development studies.**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study presented by CMI for Basilea Pharmaceutica.
Some effect is seen with iron concentration but was considered not clinically significant. Previous studies with chelater (not presented) gave similar to 1 dilution lower results. Sponsor proceeding with standard CLSI CAMHB.

Drug Name:	**BAL30072-Meropenem**			
Table 6 information:	**Solvent:** **BAL30072: DMSO** **Meropenem: Water**	**Diluent: BAL30072 DMSO and Meropenem: Water**		
Table 6C information if applicable:	**Combination Tested:** **1:1 fixed ratio**	**Preparation: Prepare each stock at 2X final concentration require for dilution series. Add equal amounts of each agent to prepare the stock solution of the combination.** **This stock may be diluted to working concentrations with water or broth.**		**Example: BAL stock:3200, meropenem stock 3200.** **Add equal volumes of each to prepare combination BAL 1600/ meropenem 1600 stock.** **Further dilute with water or broth to get to working or final concentrations.**
Glossary information:	**Class: monoclyclic β-lactam/carbapenem**	**Subclass: sulfactams/carbapenem**	**Agent Abbreviation: TBD**	**Route of Administration: TBD**

QC Strain (ATCC)	QC Range Approved mm or dil	WG Vote: Y/N/A/ NP	% in Range	Mode/ Median	# mm or dilutions	Shoulder %	Footnote to add with drug/range	Variability/Comments
***E. coli* 25922**	**0.015-0.06**	**No Vote**	**99.6%**	**0.03**	**3**	**<10%**		**RF: 0.03-0.06 (100%, 2 dil)**
***P. aeruginosa* 27853**	**0.25-1**	**No Vote**	**100%**	**0.5**	**3**	**<25%**		**RF: 0.25-1 (100%, 3 dil)**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study presented by CMI for Basilea Pharmaceutica
The MIC and concentrations are expressed as the sum of the concentration of the 2 components which is different than other compounds.
Requested input from Methods Working Group on expression of concentrations and MICs.

Vote of 7/3/2/1 NOT to approve QC ranges for BAL30072-meropenem combination at this time. Ask the sponsor for clarification on delivery/concentrations and additional QC options to control for individual drugs .
Note: While QC ranges were not approved, there were no concerns voiced about the data presented for the QC organisms tested. Therefore this data could be resubmitted when the question is addressed on how to describe the MIC and concentrations tested and providing additional QC option to QC the BAL portion of the combination.

Appendix B. Continued

Follow up on previously approved QC ranges.
Delafloxacin: Will add fuzzy zone comments to Troubleshooting Guide in 2016 since it affects multiple drugs and wording needs to be refined.

Drug Name:	**Amikacin/Fosfomycin (5:2)**			
Table 6 information:	**Solvent: Amikacin - Water, Fosfomycin—Water**	**Diluent: Amikacin - Water, Fosfomycin—Water**		
Table 6C information if applicable:	**Combination Tested: Fixed ratio of 5:2**	**Preparation: Add footnote to agent on Table 6C. Media should be supplemented with 25 mg/mL of glucose-6-phosphate.**		**Example:**
Glossary information:	**Class: Aminoglycoside/fosfomycin combination drug**	**Subclass: N/A**	**Agent Abbreviation: AKF (need to confirm with Bill Brasso)**	**Route of Administration: TBD**

Drug Name:	**Cefepime/ Tazobactam @ fixed 8 µg/mL (Previous WCK 4282)**			
Table 6 information:	**Solvent: Cefepime - Phosphate buffer. Tazobactam-water**	**Diluent: Cefepime - Phosphate buffer. Tazobactam-water**		
Table 6C information if applicable:	**Combination Tested: Tazobactam @ fixed 8 µg/mL**	**Preparation: No special instructions**		**Example:**
Glossary information:	**Class: B-lactam/β-lactamase inhibitor combination**	**Subclass: N/A**	**Agent Abbreviation: FPZ (need to confirm with Bill Brasso)**	**Route of Administration: TBD**