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Summary Minutes
Subcommittee on Antimicrobial Susceptibility Testing
Tempe Arizona
10-12 January 2016

A meeting of the CLSI Subcommittee on Antimicrobial Susceptibility Testing was held on 10-12 January 2016, at the Mission Palms Hotel, Tempe, Arizona. The following were in attendance:

Jean B. Patel, PhD, D(ABMM) **Chairholder**	**Centers for Disease Control and Prevention**
Melvin P. Weinstein, MD **Vice Chairholder**	**Rutgers Robert Wood Johnson Medical School**
Richard B. Thomson, Jr., PhD, D(ABMM), FAAM **Expert Panel on Microbiology** **Chairholder**	**Evanston Hospital, NorthShore University HealthSystem**

Members Present

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
Amy J. Mathers, MD	University of Virginia Medical Center
Tony Mazzulli, MD, FRCPC, FACP	Mt. Sinai Hospital, Toronto
Robin Patel, MD	Mayo Clinic
Sandra S. Richter, MD, D(ABMM)	Cleveland Clinic
Michael Satlin, MD, MS	Weill Cornell Medical College
John D. Turnidge, MD	Australian Commission on Safety & Quality in Healthcare
Barbara L. Zimmer, PhD	Beckman Coulter Microscan

Advisors Present

Jeff Alder, PhD	Bayer
Patricia A. Bradford, PhD	AstraZeneca Pharmaceuticals
William B. Brasso	BD Diagnostic Systems
Rafael Canton	EUCAST/ESCMID
Graeme Forrest	Portland VA Healthcare System
Janet A. Hindler, MCLS, MT(ASCP)	UCLA Medical Center

Romney M. Humphries, Ph.D., D(ABMM)	UCLA David Geffen School of Medicine
Thomas J. Kirn, Jr., MD, PhD	Rutgers Robert Wood Johnson Medical School
Linda A. Miller, PhD	GlaxoSmithKline
Melissa B. Miller, PhD, D(ABMM)	UNC School of Medicine
Greg Moeck, PhD	The Medicines Company
Sumathi Nambiar, MD, MPH	FDA/CDER
David P. Nicolau, PharmD, FCCP, FIDSA	Hartford Hospital
James Ross	JMI Labortories
Helio S. Sader, MD, PhD	JMI Laboratories
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)
Pranita D. Tamma, MD, MHS	Johns Hopkins University School of Medicine
Kazuhiro Tateda, MD, PhD	Toho University
Maria M. Traczewski, BS, MT(ASCP)	The Clinical Microbiology Institute

Reviewers Present

April Abbott	Deaconess Health System
Robert Badal	IHMA, Inc.
Lynn Boyer	Beckman Coulter
Steven D. Brown, PhD, ABMM	Consultant
Carey-Ann Burnham, PhD, D(ABMM)	Washington University School of Medicine
Karen Bush, PhD	Indiana University
Diane M. Citron, M(ASCP), BS	R.M. Alden Research Laboratory
Patricia S. Conville, MS, MT(ASCP)	FDA/CDRH
Sharon K. Cullen, BS, RAC	Beckman-Coulter
Linsey Donner	The Nebraska Medical Center
Michael J. Dowzicky	Pfizer Inc
German Esparza, BSc	Proasecal Sas Columbia
Robert Eusebio, MSHA, MT(ASCP)	Beckman Coulter
Gina L. Ewald-Saldana, CLS(CA), MT(ASCP)	Beckman Coulter
Mary Jane Ferraro, PhD, MPH	Massachusetts General Hospital
Robert K. Flamm, PhD	JMI Laboratories
Flavia Rossi, MD	University of Sao Paulo
Barb Gancarz	bioMerieux, Inc.
Beth P. Goldstein, PhD	Beth Goldstein Consultant
Meredith Hackel	International Health Management Associates, Inc.
Stephen Hawser, PhD	IHMA Europe
Patricia Hogan, MT(ASCP), MBA	Pfizer Inc
Michael D. Huband	JMI Laboratories
Jack L. Johnson	IHMA, Inc.

James H. Jorgensen, PhD	University of Texas Health Science Center
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
Joseph Kuti, PharmD	Hartford Hospital
Sarah Blaine Leppanen	Blaine Healthcare Associates Inc.
Dyan Luper, BS, MT(ASCP)SM	BD Diagnostic Systems
Linda M. Mann, PhD, D(ABMM)	Clinical Microbiologist, Consultant
SandraMcCurdy	Melinta Therapeutics, Inc
Ian Morrissey, MBA, PhD, FRSM	IHMA Europe Sa…rl
Mary R. Motyl, PhD, D(ABMM)	Merck & Company, Inc.
Susan D. Munro, MT(ASCP)	Consultant
Cathy A. Petti, MD	University of South Florida
Susan O'Rourke	BD
Elizabeth Palavecino, MD	Wake Forest University Baptist Medical Center
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
Daniel F. Sahm, PhD	International Health Management Associates, Inc.
Dale A. Schwab, PhD, D(ABMM)	Quest Diagnostics, Nichols Institute
Katherine Sei	Beckman-Coulter
Sharon Shinn	Siemens Healthcare Diagnostics Inc.
Dee Shortridge, PhD	BioMerieux, Inc.
Thomas R. Shryock, PhD	Antimicrobial Consultant, LLC
Judith N. Steenbergen, PhD	Merck
Laura Stewart	BD
Gregory G. Stone	AstraZeneca Pharmaceuticals
Jana Swenson	
Ben Turng	Accelerate Diagnostics Inc.
Hui Wang, PhD	Peking University People's Hosptial
Wayne F. Wang, MD, PhD	Emory University Hospital
Nancy Watz	Stanford Hospital and Clinics
Matthew A. Wikler, MD, MBA, FIDSA	
Mary K. York, PhD, ABMM	MKY Microbiology Consulting

Observers Present

Kitty Anderson	CDC
Stella Antonara	Nationwide Children's Hospital
Lynette Berkeley	FDA
April Bobenchik	Rhode Island Hospital/Brown University
Malcom Boswell	Accelerate Diagnostic
Linda C. Bruno, MA, MT(ASCP)	ACL Laboratories

Susan Butler-Wu	LAC/USC Medical Center
Davina Campbell	CDC
Angella Charnot-Katsikas	University of Chicago
Karissa Culbreath	University of New Mexico
Tanis Dingle	Mount Sinai Hospital
Dana Dressel	IHMA, Inc.
Roger Echols	Shionogi
Sheila Farnham, MT(ASCP)	bioMerieux
Mark Fielder	Kingston University
Mark Fisher	U. Utah/ARUP Labs
Andrea Gagh	Thermo Fisher
Alice Gray	bioMerieux
Trudy Grossman	Tetraphase Pharmaceuticals
Christine Hastey	Beckman Coulter
John Hejna	BD Diagnostic Systems
Nicole Holliday	Thermo Fisher Scientific
Andre Hsiung	Hardy Diagnostics
Nicole Hunter	Thermo Fisher
Joseph Iaconis	Astra Zeneca
Seong Jang	FDA
Kristie Johnson	University of Maryland
Ron Jones, MD	JMI
Nachum Kaplan	Nobelex Biotech
Maria Karlsson	CDC
Aryan Kim	Genetech
Melinda Lacy	Theravance BioPharma
Xian-Zhi Li, PhD	Health Canada Veterinary Drugs
Joseph Lutgring	Emory University
Maureen Mansfield	
Erika Matuschek	EUCAST
Sally Maysent	Thermo Fisher
Sarah McLeod	Entasis Therapeutics
Alita Miller	Entasis Therapeutics
Shelly Miller	UCLA
Timothy Morris	Actelion Clinical Research
Ross Mulder, MT(ASCP)	bioMerieux, Inc.
Kiyofumi Ohkusu	Tokyo Medical University
David Paisey	Thermo Fisher Scientific
Christine Pallotta	Thermo Fisher Scientific
Virginia Pierce	Massachusetts General Hospital
Chris Pillar	Microruyx
Shannon Popson	Beckman Coulter
Violeta Rekasius	Loyola University Medical Center
Denis Robichon	Debiopharm
Nilia M. Robles Hernandez	bioMerieux, Inc.
Nicole Scangarella-Oman	GlaxoSmithKline
Alisa Serio, PhD	Achaogen
Rosemary She	USC
Carole Shubert	bioMerieux, Inc.

Patricia Simner	Johns Hopkins
Jennifer Smart	Theravance BioPharma
Christopher Tan	Merck & Co.
Jolyn Tenllado	bioMerieux, Inc.
Susan Thomson	MAST Group
Masakatsu Tsuji, PhD	Shiongi & Co. Ltd
Ken VanHorn	Kindred Hospital
Marzena Wal	Anaheim Regional Medical Center
Linda Weigel	CDC
Anne Windau	Laboratory Specialist
Sarah Wood	Beckman Coulter
Yoshinori Yamano, PhD	Shionogi & Co. Ltd
Katsunori Yanagihara, MD, PhD	Nagasaki University
Lynn Yaolin	Allergan Inc.
Katherine Young	Merck

CLSI Staff

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

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I. MEETING/OPENING REMARKS

Dr. Jean Patel called the meeting to order at 12:30 p.m. on Monday, 11 January 2016. She welcomed everyone and thanked all the working groups (WG) for the all the work done at this meeting as well as the continual work being done outside of the January and June meetings, making this meeting more efficient.

Dr. Patel discussed the recent changes to the subcommittee including Dr. Mel Weinstein assuming the role as the new Vice Chairholder for the Subcommittee. She then acknowledged Dr. Frank Cockerill who had served first as Chairholder then Vice Chairholder of the Subcommittee, and the many contributions to the work of this committee during this time.

Other changes to the Subcommittee includes:

New Voting Members:

- Amy Mathers, MD – from University of Virginia Medical Center
- Tony Mazzulli, MD, FRCP (C), FACP – from Mt. Sinai Hospital
- Michael Satlin, MD, MS – from Weill Cornell Medical College/ NewYork-Presbyterian Hospital

New Advisors:

- Thomas J. Kirn, Jr., MD, PhD - from Rutgers Robert Wood Johnson Medical School
- Greg Moeck, PhD – from The Medicines Company
- Kazuhiro Tateda, MD, PhD – from Toho University School of Medicine

Other rotations/changes:

- David P. Nicolau, PharmD, FCCP, FIDSA – rotated from member to advisor and continues as an active participant of not only the subcommittee but also the Breakpoint Working Group
- Mair Powell, MD, FRCP, FRCPath –due to difficulties to attend meetings, Dr. Powell asked to resign from the subcommittee.

Advisors who rotated to reviewers:

- Dwight Hardy, PhD – has participated on the subcommittee as a voting member, as an advisor and has also chaired WGs in the past and recently agreed to Co-Chair the Methods Development and Standardization WG.

- Mike Dudley, PharmD, FIDSA – has made many tremendous contributions over that years participating on the subcommittee as a voting member, as an advisor and as Chairholder of the *Enterobacteriaceae* WG during a very critical time of reviewing and changing breakpoints.
- Cathy Petti, MD – had served as an advisor on the subcommittee and continues to work as Co-Chairholder of the Molecular Detection of AR Ad Hoc WG

- Hui Wang, PhD – had served as an advisors on the subcommittee and continues to be a member of the Breakpoint WG

- Kerry Snow, MS, MT (ASCP) – had served as an advisor on the subcommittee and has since retired from FDA.

II. CLSI UPDATE

Mr. Glen Fine, CEO of CLSI welcomed everyone and thanked the Subcommittee for their continued time and work from all experts that participate throughout the year and also contribute so much during meetings.

Mr. Fine then introduced CLSI staff present at the meeting as follows:

- Tracy Dooley – Senior Program Manager and Liaison to the Expert Panel on Microbiology;
- Marcy Hackenbrack – Senior Project Manager and Liaison to the Expert Panel on Molecular Methods who also assists with various projects under microbiology;
- Angela Miller – Director of Standards Development; and
- Stephanie Robinson – Meeting Manager who coordinates all the logistics for these meetings.

What's New:

- This year CLSI will be making M100 freely available in an electronic viewable format of the document on the CLSI website. There will be a link available on the homepage of the CLSI website that will take you directly to this free version. M100 is also available for purchase as a hard print copy (blue books), as a PDF download, and as a searchable on-line access version that is customizable.

  CLSI will also be making the Veterinary supplement VET01 available in a free on-line version and in the Spring of this year the supplements developed by the Antifungal Subcommittee will be available as well. These supplements are being updated and once published, will be available on the CLSI website.

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. The following updates will be added to the DOI summary: Amy Mathers – add Accelerate Diagnostics; David Nicolau – add Shionogi; and Sandy Richter – add Roche.

IV. APPROVAL OF THE JUNE 2015 MEETING MINUTES

Summary minutes of the 14-16 June 2015 subcommittee meeting were approved: **(10-0; 1 absent)**

V. REPORT OF THE TEXT AND TABLES WORKING GROUP *(*Electronic Folder 5)

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

Members Present: Janet Hindler, Peggy Kohner, Dyan Luper, Linda Mann, Melissa Miller, Susan Munro, Flavia Rossi, Dale Schwab, Tom Thomson, Nancy Watz, Mary York

Members absent: None

ITEMS FOR VOTE:

1. Q&A and revisions to Table 2C comments (4) and (14):

A question was received by CLSI asking how Table 2C comment (14) should be interpreted, ie, how should non-*epidermidis* CoNS with oxacillin MICs of 0.5 to 2 μg/mL that test susceptible by cefoxitin or are negative by mecA/PBP2a be reported. Discussion of the WG centered on whether these strains should be reported as oxacillin susceptible or whether we should just recommend that oxacillin be considered for treatment. The WG agreed unanimously that oxacillin should be reported as susceptible.

The Q&A proposed by the WG is as follows:

> **Table 2C** contains a comment (14) on the interpretation of MICs from CoNS excluding S. *lugdunensis* indicating that some strains with MICs in the range of 0.5-2 μg/ml [Resistant] lack the *mecA* gene and PBP2a and that for these isolates, testing for these markers or performing a cefoxitin disk diffusion may be appropriate. But the document does not offer guidance as to how to report organisms with MIC's in this range for which the test for mecA/PBP2a is negative. Are these organisms to be considered susceptible for clinical purposes in view of the absence of *mecA* or are they to be reported resistant due to the possibility of alternative mechanisms of resistance as indicated in comment (4) in the same Table? Please advise.

- Comment (14) was included because it was determined that for some species of CoNS other than *S. epidermidis*, strains with MICs between 0.5 – 2 μg/mL (interpreted as R using CoNS criteria but S using SA criteria) may be *mecA* negative. Therefore the SA breakpoints appeared to be more useful for those strains. However, at the time most clinical laboratories did not have the capacity to identify CoNS to the species level. In the publication where these organisms were identified (JCM 37:4051-4058, 1999), the conclusion stated was "Whether strains of CoNS (other than *S. epidermidis*) for which oxacillin MICs were in the range of 0.5 to 2.0 μg/ml would be eradicated with penicillinase-resistant penicillins remains an open question." They further stated that "Decreased susceptibility to oxacillin in these isolates may be due to alterations in penicillin binding proteins (PBPs) other than PBP2. For example,

Suzuki et al. (AAC 36:429-434, 1992) reported changes in PBPs 1 and 4 in several strains of methicillin-resistant, *mecA*-negative *S. haemolyticus* and *S. saprophyticus*." However, for strains of CoNS other than *S. epidermidis* with MICs between 0.5 and 2 µg/mL that test *mecA/*PBP 2a negative or cefoxitin susceptible, oxacillin should be reported as susceptible.

Following this, revisions were recommended for comments (4) and (14) as follows:

(4) ~~In most staphylococcal isolates,~~ Most oxacillin resistance is mediated by *mecA*, encoding the penicillin-binding protein 2a (PBP 2a, also called PBP2'). Isolates that test positive for mecA or PBP 2a should be reported as oxacillin resistant.

S. aureus and CoNS ~~I~~isolates that test resistant by oxacillin MIC (MIC ≥ 4 µg/mL), cefoxitin MIC, or cefoxitin disk test should be reported as oxacillin resistant. For non-*epidermidis* CoNS with oxacillin MICs between 0.5 and 2 µg/mL, see comment (14).

Mechanisms of oxacillin resistance other than *mecA* are rare and include a novel mecA homologue, mecC.[1] MICs for strains with *mecC* are typically in the resistant range for cefoxitin and/or oxacillin; *mecC* resistance cannot be detected by tests directed at *mecA* or PBP 2a.

(14) 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. For these strains that test mecA/PBP 2a negative or cefoxitin susceptible, oxacillin should be reported as susceptible.

The SC approved the Q&A and the comment revisions 10-0; 1 absent.

ITEMS FOR INFORMATION ONLY:

2. Revision of M02/M07 for publication in 2018:

An ad hoc working group was formed to revise M02 and M07. The ad hoc group is co-chaired by Ms. Susan Munro and Dr. Carey-Ann Burnham. Members include: Christopher Doern, Recording Secretary, Patricia Conville (FDA Ctr. For Devices/Rad. Health), Dwight Hardy (Univ. of Rochester Medical Center, Susan Kircher (BD Diagnostics), Margaret Ordonez (Microbiology Institute of Columbia), Yun Wang (Emory Univ. Hospital), and Alexandra Wang (FDA Ctr. For Devices/Rad. Health).

- The highlights of the timeline for revision are to continue review and revision through 2016. Then a near-complete draft will be reviewed by Text and Tables WG in Jan. 2017. A final draft should then be included in the June 2017 agenda book for publication in Jan. 2018.

3. Report of the Outreach Working Group:

Ms. Janet Hindler reported on the various activities of the group, including a biannual newsletter, planned webinars, and educational tools being developed. During discussion of revisions being considered for M02 and M07, it was decided that it would be useful to create a document or module on antimicrobial agents to include mechanisms of action and resistance and that the Outreach group would be a good place to coordinate this. A request for anyone who might be interested in helping with this was made; those interested should contact Ms. Janet Hindler or Dr. Audrey Schuetz.

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: Amy Mathers, David Nicolau, Mair Powell, Michael Satlin, Audrey Schuetz, Lauri Thrupp*, Hui Wang, Mel Weinstein,

Technical Advisor Present: Matt Wikler

Members Absent: Marcelo Galas, Paul Schreckenberger, Simone Shurland, Barbara Zimmer

* Joined by conference call on 10 January 2016

The following topics were presented and discussed.

1. Viridans Streptococci/ Penicillin Reporting for Endocarditis (files 6 0 thru 6 3)

Ms. Jana Swenson presented background information concerning the reporting of MICs of 0.125 µg/mL or 0.12 µg/mL for penicillin. CLSI breakpoints are ≤0.12 µg/mL (S) and 0.25 µg/mL (I); the EUCAST susceptible breakpoint is ≤0.125 µg/mL. Dr. Butler-Wu at the Univ. of Washington reported that at her institution, penicillin MICs of 0.125 µg/mL were being reported as I, not S. It was explained that CLSI uses the convention of reporting the concentration of 0.125 µg/mL as 0.12 µg/mL, so the interpretive criteria were not being reported accurately. During the discussion, it was noted that for Etest analyses, 0.125 µg/mL should also be reported as 0.12 µg/mL.

The following wording was proposed to be added in Table 2H-2 as new comment (6):

If penicillin is tested as 0.125 µg/mL, it should be reported as 0.12 µg/mL. See Instructions for Use of Tables, Section II.

Add as last part of number 6. Interpretive Criteria in Section II of Instructions for Use of Tables:

When serial 2-fold dilution MICs are being prepared and tested, the actual dilution scheme is:

128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.0625, 0.03125, 0.015625, 0.0078125, 0.0039063, 0.0019531 µg/mL, etc.

For convenience only and not because these are the actual concentrations tested, it was decided

to use the following values in the Tables:

128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03, 0.015, 0.008, 0.004, 0.002 µg/mL, etc.

Subcomittee Vote – Approved 10-0; 1 absent

A later suggestion was made to broaden this wording for all drugs that are tested at 0.125 µg/mL. The Text & Tables WG will review where this may also apply in M100.

2. Colistin/Polymyxin B Ad hoc WG (files 1 0 and 1 1)

Dr. John Turnidge presented an update regarding colistin breakpoints for nonfermenters based on the June 2015 request to try to harmonize CLSI and EUCAST breakpoints for *P. aeruginosa* (and *Acinetobacter*).

Current colistin breakpoints for *Pseudomonas aeruginosa* are:

CLSI ≤2 µg/mL (S); 4 µg/mL (I); ≥8 µg/mL ((R)
EUCAST ≤4 mg/L (S); >4 mg/L (R)

Dr. Turnidge proposed breakpoints for *P. aeruginosa* and *Acinetobacter*:

CLSI ≤2 µg/mL (S); ≥4 µg/mL (R)
EUCAST ≤2 mg/L (S); >2 mg/L (R)

Discussion points:

- PK/PD doesn't support a breakpoint >0.5 µg/mL. Dr. Turnidge says lowering the breakpoint that low would greatly diminish the use of colistin for *P. aeruginosa* where it is used frequently, especially in combination therapy. A recent MIC distribution (June 2015, CLSI appendix 5.0) showed <30% of the 2015 *P. aeruginosa* isolates in the EUCAST database had colistin MICs ≤0.5 mg/L. The modal MICs for colistin were 0.5 mg/L for *Acinetobacter* and 1.0 mg/L for *P. aeruginosa*. It was suggested that a breakpoint of 2 mg/L would allow the use of colistin in combinations, which could be a part of the accompanying comments. An Intermediate designation may not be a viable option, as colistin can't be dosed higher.

  - A motion was made to approve the following breakpoints for colistin that would harmonize breakpoints with EUCAST for *Pseudomonas aeruginosa* and *Acinetobacter*.

    Colistin: ≤2 µg/mL (S); ≥4 µg/mL (R) - The motion passed - **Subcommittee Vote - Approved 8-2; 1 absent** (Disk breakpoints for colistin/*P. aeruginosa* will be deleted)

  - A subsequent motion was made to include additional language such as "Considering the limitations of the susceptibility testing methodology, maximal dosing and/or combination therapy should be considered." The specific phrasing should be proposed in collaboration with EUCAST that is considering a similar statement. The motion was approved by the WG:

    WG Vote = 11 Yes, 0 No, 0 Abstain

3. *B. anthracis*/Penicillin Ad Hoc WG - Drs. Linda Weigel and Jim Jorgensen, chairs (files 2 0 thru 2 5).

A request was made by the CDC to reassess the interpretive criteria for susceptibility of *Bacillus anthracis* to penicillins. The current CLSI penicillin susceptibility breakpoint is 0.12 µg/mL (in CLSI document M45). Major points of the discussion follow:

- Dr. Weigel presented recently determined penicillin MIC distribution for 52 strains of *B. anthracis*. Of these 52 strains, five and one strain had penicillin MICs of 0.25 and 0.5 µg/mL, respectively; five strains had penicillin MICs >256 µg/mL. Laboratory data demonstrate the β-lactamases in *B. anthracis* are not inducible; however, a few hyperproducing β-lactamase strains exist with very high penicillin MICs (>256 µg/mL).
- Variability in MICs can be seen for a subset of strains, with MICs ranging from 0.03 to 0.5 µg/mL when the same strain is tested on different days.
- Amoxicillin, frequently recommended for prophylactic dosing for anthrax, has MICs approximately 2-fold lower than penicillin with less day-to-day variability in MIC testing.
- Addition of β-lactamase inhibitors to amoxicillin and ampicillin lowers the MICs for both amoxicillin (amoxicillin-clavulanic acid) and ampicillin (ampicillin-sulbactam). Because no PK/PD information to support patient dosing was available, no recommendation was made to include these in the CLSI table.
- Dr. Jorgensen proposed the following breakpoints from the ad hoc WG for penicillin and amoxicillin against *B. anthracis.* A motion to accept these was approved to be changed/added in CLSI document M45 Table 21.

	S	I	R
Penicillin	≤0.5 µg/mL		≥1 µg/mL
Amoxicillin	≤0.12 µg/mL		≥0.25 µg/mL

Subcommittee Vote - Approved 10-0; 1 absent.

- Although the WG suggested a comment about defining amoxicillin as the preferred penicillin for susceptibility testing, the CDC requested that this not be included.
- A motion was made and passed to move the following items to Text and Tables.
  - Strike the comment that isolates S to penicillin are S to amoxicillin.
  - Delete comments 9 and 10.
  - Add a comment: "Amoxicillin may be considered for prophylactic use in children and pregnant or lactating women."

4. *Gonorrhea* Ad hoc Working Group. Drs. John Papp and Mary Jane Ferraro (files 3 0 and 3 1).

The CDC suggested that CLSI and EUCAST try to harmonize breakpoints for azithromycin, cefixime, ceftriaxone and ciprofloxacin for *Neisseria gonorrhoeae.*

- In an informational discussion Dr. Ferraro listed several ECV (Epidemiological Cut-off Value) issues: explanation for azithromycin MICs of ≥1 µg/mL; unknown correspondence of ceftriaxone MICs with mosaic PBPs; calculation of ECVs following collection of all data.
- Questions were raised as to whether there was a problem with clinical failures. Do we really need to lower the MICs for useful drugs that are currently being used successfully?
- Answer: An attempt will be made to balance the desire to know the ECV that can be used for surveillance, with the inclination to lower breakpoints to this level, especially for isolates that don't have known resistance mechanisms.
- The group was cautioned not to lower MICs too far to make currently useful drugs unusable.

5. Fluoroquinolone/*Salmonella* Ad hoc WG to discuss the use of nalidixic acid as a surrogate for fluoroquinolone testing in *Salmonella* spp. Ms. Janet Hindler and Dr. Amy Mathers (files 5 0 thru 5 6).

Amy Mathers provided the following summary from the ad hoc WG. The ad hoc WG moved to remove Nalidixic acid disk test as a surrogate for fluoroquinolone susceptibility from the document. They recommended adding a comment in a supplement/appendix, explaining the rationale.

- Discussion from the BP WG:
  - Many people use nalidixic acid to test for extraintestinal isolates. Although there are problems with testing ciprofloxacin at low concentrations for MIC testing, ciprofloxacin disks are available for testing and perform better than nalidixic acid disks.
  - There are problems obtaining pefloxacin disks (as a surrogate) in US.

- Two suggestions were made for the Text and Tables WG
  - Place a comment in the table for those who are still using nalidixic acid for testing, but do not list breakpoints.
  - OR, Move the test from the table into an appendix with the rationale.

    – The BP WG moved and approved the following motion: Accept the Ad hoc WG proposal to remove nalidixic acid test from Table 2A and add a comment.
    WG Vote = 9 Yes; 1 No; 0 Abstain.

    – A second motion was made and passed: The wording and placement of the nalidixic acid comments should be transferred to the Text and Table WG.
    WG Vote = 10; 0 No; 0 Abstain

    – In the discussion, the poor performance of the pefloxacin disk as a predictor of resistance was reported by Dr. M. Galas in Latin American isolates, apparently due to media variability. A motion was made and approved to add a new *Salmonella* QC strain with a low level resistance mechanism. WG Vote = 10; 0 No; 0 Abstain

- **Subcommittee**: A motion was made and approved by the subcommittee to remove nalidixic acid from Table 2A for *Salmonella* spp. and place in a new Appendix as a retired test with information explaining why nalidix acid testing is not done. Comments will be added in Table

2A such as those shown below, with the final wording to be provided by the Text and Tables WG **Subcommittee Vote - Approved 10-0; 1 absent**:

(XX) The preferred test of assessing fluoroquinolone susceptibility or resistance in *Salmonella* spp. is a ciprofloxacin MIC test. A levofloxacin or ofloxacin MIC test can be performed if either agent respectively is the fluoroquinolone of choice in a specific laboratory. Alternative tests as described below can be used with an understanding of their limitations.

(XX) If pefloxacin is tested, report the data as fluoroquinolone susceptible or resistant based on pefloxacin testing. Note that this will not predict resistance due to *aac(6')-Ib-cr*.

- A suggestion was made that the WG should examine ciprofloxacin-I isolates to determine how to improve guidance in the document in the setting of reported clinical failures in this range.

6. Fluoroquinolone (FQ)/*Enterobacteriaceae* Ad hoc WG to review the Fluoroquinolone Breakpoint Report published by USCAST. Drs. Mel Weinstein and Mary Jane Ferraro (files 4 0 thru 4 3).

A summary of the discussion follows;

- The ad hoc WG appreciated the large amount of effort put into the USCAST document that was presented to EUCAST last summer as well as to CLSI this winter. Dr. Ron Jones volunteered background on the report that began as a PK/PD re-evaluation of FQ breakpoints, and ended up as a 244 page document. He indicated that the group will move on to aminoglycosides next and then the polymyxins.
- The WG group put together a list of questions to clarify questions and issues raised by the USCAST document and asked participants for guidance.
- Representatives from USCAST were present but did not provide detailed responses to each of the written WG questions. They indicated that they accomplished their goal of getting CLSI to consider re-evaluation of fluoroquinolone breakpoints. A summary of their points were:
    - Much of the PK/PD interpretations are based on Dr. W. Craig's data that have been the basis for many of the CLSI breakpoint decisions in the past.
    - Human PK data was obtained from literature sources, or package inserts when possible.
    - It's now up to CLSI to determine whether M23 conditions have been met.

- Dr. Rafael Canton stated that EUCAST is in the process of updating breakpoints and the process is not complete. It will take at least 2 more EUCAST meetings to finalize these, so there is currently no "harmonization" that can take place.

The BP WG continued discussion:

- It is now up to this group to decide whether M23 criteria have been met.
- A looming question was whether clinical data exist to demonstrate clinical failures in *Enterobacteriaceae* which have occurred due to FQ breakpoints that are too high? Because there is heavy use of fluoroquinolones, it is important to be sure the CLSI recommendations are

correct. For example, recent publications state that ciprofloxacin is the second most used antibiotic in the US (Dr. Ron Jones). However, this examination would take great effort and therefore consideration of the impact on clinical outcomes would inform prioritization of revisiting the FQ Enterobacteriaceae breakpoints.

- Only one published report on FQ clinical failures was identified (DeFife et al, AAC 53:1074, 2009; CLSI file 4.3), but the levofloxacin doses were 500 mg, not the currently recommended 750 mg dose. Also, many of the isolates in the study were *Pseudomonas*; only 10/21 isolates with high levofloxacin MICs were *Enterobacteriaceae*.
- A suggestion was made to look for recent clinical trial data in which fluoroquinolones have been used as the comparative agent, but the doses should be those currently utilized.
- There was a reminder that clinical trial data represent only one factor to consider in changing a breakpoint.
- A suggestion was made that, as CLSI considers these data and breakpoint proposals from USCAST, CLSI should try to harmonize with EUCAST (which is also considering this proposal) and with FDA.
- Perhaps FQ breakpoints are a bigger issue with *Pseudomonas*, not *Enterobacteriaceae*.

BP WG summary:

- Fluoroquinolones are often used empirically. Breakpoints should be examined. In all these analyses, it is important to look for exposure/response relationships as clinical data are mined.
- The WG should look for recent clinical data.
- In June, the AST should determine whether FQ BPs for *Enterobacteriaceae* need to be changed. By then, EUCAST may have finalized their data so that harmonization could be considered.

VII. REPORT OF THE METHODS APPLICATION AND INTERPRETATION WORKING GROUP (Electronic Folder 7)

Co-Chairholder - Brandi Limbago
Co-Chairholder - Stephen Jenkins
Recording Secretary – Patricia Simner

Members Present: Darcie Roe-Carpenter (Text & Tables Liaison), Sandra Richter (Text & Tables Liaison), J. Kristie Johnson, Joe Kuti, Susan Sharp, Ribhi Shawar

January 10, 2015 (3:30-5:30 pm) WG Session; Part 1

1. Introduction of group and new members
2. Discussed the division of the responsibilities for the Methods Group into two entities:
   a. Methods Development and Standardization - Drs. Zimmer and Hardy co-chairs
   b. Methods Application and Interpretation - Drs. Jenkins and Limbago co-chairs

3. The WG entertained a report from the Surrogate Testing ad hoc WG explaining their final decisions and reviewed the materials included in this year's M100 document published in January 2016.

a. Discussion ensued as to why surrogate antibiotics may be tested?
   - If the surrogate generates a more accurate answer; e.g., cefoxitin to predict oxacillin
   - If the surrogate compound is more readily available or the drug to be reported is not readily available.
   - The ad hoc WG had been asked to define screening tests and re-write applicable sections of M100 accordingly. The recommendations from the ad hoc WG defined surrogate, screening, and supplemental testing and were approved by the subcomittee for inclusion in M100-S26 as new Section VII.

b. The new tables were drafted and proposed by Romney Humphries and Janet Hindler and included:
   - Screening: A sensitive test that needs confirmation
     - Discussion surrounded the fact that presumptive positive results need confirmatory testing and the WG suggested that the definition should be made clearer
     - If negative, no further testing is required. If positive – confirmatory testing is required. Suggestion to add to the definition: "If screen is negative, no further testing is required."
   - Surrogate: An agent that replaces testing of an agent of interest that cannot be tested due to performance issues or if it performs better than the agent of interest
   - Equivalent agents: an agent that predicts results to closely related agents; e.g., cefotaxime or ceftriaxone; azithromycin/clarithromycin/erythromycin for many organisms such as pneumococci
   - Supplemental: a test that detects susceptibility or resistance to a drug or drug class by method other than routine AST; e.g., ESBL confirmatory testing or Carba NP testing
   - Table location should be in each of the additional tables (example: the supplemental tests table). This will be added for the next edition of M100.
   - Clear up definition/editorial issues. Make the table inclusive of all examples and add it as an exhaustive table to the back of the M100.
   - The WG needs clarification as to whether the tables were meant to be all- inclusive or just list examples of each. A recommendation was made to add the Table location column to each of the individual tables.

4. The WG considered a Report on the recommendations from the Molecular Results Reporting ad hoc WG – Drs. Tom Kirn and Cathy Petti – Co-Chairholders

   Three tables were presented for discussion and consideration: *Enterobacteriaceae, S. aureus* and Enterococci:

   a. *Enterobacteriaceae* table
      - Integrate the *Enterobacteriaceae* table as is with the word 'consider' in the reporting section (soften the wording)
        - J. Kuti made a motion to approve the document with softened language; e.g., add the word "consider" in the reporting of discordant results as resistant when molecular tests indicated the presence of an ESBL, but phenotypic tests did not confirm the finding (S. Richter seconded the motion). WG vote: 6 Approved, 1 Opposed, 2 Abstaining (motion

passed) B. Limbago opposed the motion due to the fact that it contradicts the current guidance. The WG recommended that references to the footnotes be added, if available. Motion made by D. Roe-Carpenter; seconded by B. Limbago WG Vote: 8 approved; 0 opposed; 0 abstained (motion passed).

Subcommittee Vote: The subcommittee accepted the table concept with some edits and requested that it be brought back to the subcommittee in June. It was suggested to also add an introduction for the table. **Approved 7-3; 1 absent**.

b. MRSA table
   - S. Sharp moved that the MRSA table move forward to the subcommittee as is. S. Jenkins seconded the motion. WG **Vote: 8 approved/0 opposed/0 abstained - The motion Passed**

   Subcommittee Vote: **Approved 10-0; 1 absent**

c. VRE table
   - Standardize the surveillance vs screening culture language between the MRSA and the VRE tables. The WG recommends the use of "surveillance specimens" in the Table.
   - Consider reporting molecular results throughout the tables consistently. Remove the words 'presence of molecular target.'
   - S. Sharp moved that the MRSA table move forward to the full subcommittee as is. S. Richter seconded the motion. **WG Vote: 8 approved/0 opposed/0 abstained. The motion Passed**

   Subcommittee Vote: **Approved 10-0; 1 absent**

5. The WG considered a Report from the Anaerobes ad hoc WG: Dr. Darcie Roe-Carpenter – Chairholder:

- Epidemiologic cutoff values (ECV) gram-positive anaerobes
- The ad hoc WG requested that the data be reprocessed (further divided by species, group) and that it be brought back for further discussion at the June 2016 meeting
- Agar vs Broth data for *Clostridium difficile*
  - Merck (formerly Cubist); Laurent Chesnel presented testing data for ~900 *C. difficile* isolates by both methods
  - Broth MIC results were 1 to 3 dilutions lower than those for agar dilution, depending on the antibiotic for *C. difficile*
  - The ad hoc WG recommendation was to keep broth testing only for isolates in the *B. fragilis* group
- The ad hoc WG reviewed an update for the M11-A8 document; it will be revised further based upon agar vs broth dilution data, for potential approval in June 2016
- The Antibiogram publication was submitted to for publication.

- Breakpoint differences were noted for three antimicrobials (piperacillin-tazobactam, ertapenem, and metronidazole) between CLSI and EUCAST; the issue will be sent to the Breakpoint Working Group for assessment

6. The WG considered a Report from the ad hoc Tables 1 and 2 WG that focused on the remaining issues not fully addressed at past meetings: Dr. Mary York – Chairholder

   a. Title from Tables 1 not stated correctly – the Table title: Suggested grouping of Antimicrobial Agents with Clinical Indications, Change to:

      Table 1A. Suggested Groupings of Antimicrobial Agents ~~With~~ Approved by the US Food and Drug Administration for Clinical Use ~~Clinical Indications~~ That Should Be Considered for ~~Routine~~ Testing and Reporting on Nonfastidious Organisms by Microbiology Laboratories in the United States

      A motion was made to accept the change by S. Jenkins and was seconded by R. Shawar. **WG Vote: Approved - 9, 0 - opposed, 0 – abstained. The motion passed.**

      Subcommittee Vote: Approved above changes with the addition of the deletion of the word 'Routine' as shown highlighted above – Approved 10-0; 1 absent. This applies to Tables 1B and 1C as well.

   b. Table 1A: Look at the *Acinetobacter* spp.
      - Revisit current placement of ceftriaxone and cefotaxime in Group B - No motion was made to remove them by the WG
      - Should minocycline be moved from Group B to Group A?

        The ad hoc WG voted 6 to 2 in favor of the proposed change to move minocycline into Group A. the motion passed. Discussion ensued related to the fact that minocycline is not currently on several commercially available panels (it is on the BD Emerge panel), except for Trek, and this may encourage addition of the compound to panels. Disks are available.

        Concern was expressed that Group A guides laboratories that they should test. It was suggested to keep the drug in Group B due to minimal clinical evidence regarding its efficacy. The thought is that if they include it in Group A, it will encourage commercial manufacturers to include it in on their panels.

        S. Jenkins made a motion to add a footnote (add to Table 1A), leaving the drug in Group B (the footnote clarifying the fact that minocycline is more active than doxycycline against these organisms. Suggested verbiage was: "Minocycline is the most active of the tetracyclines". J. Kuti seconded the motion. **WG Vote: 7- approved, 1 - opposed , 1 – abstained; the motion Passed** S. Richter opposed the motion as she would like to put the footnote in the organism Table rather than in Table 1.

Subcommittee motion – accept to leave in Group B and put a footnote – **Not Approved 6-4; 1 absent. No Change will be made.**

c. *Haemophilus* spp.

– Revise footnote "d" in Table 1B. Remove chloramphenicol – moved to Group C due to lack of use in developed countries. Did not remove it completely as the drug is still used in under-developed countries.

- Changed "one of" to "any of the third-generation cephalosporins"; remove chloramphenicol and remove the word "routinely". Discussion ensued as to whether to reword the "any of the third-generation cephalosporins" – to "cefotaxime or ceftriaxone". The Package Insert for ceftazidime lists a clinical indication for *H. influenzae* meningitis.
- Footnote is also behind *H. parainfluenzae* (but this does not relate to isolates from CSF); suggested that it be moved to follow immediately after *H. influenza.*

S. Sharp made a motion to move forward with the modified version with the addition of "listed" after cephalosporins. D. Roe-Carpenter seconded the motion.

Table 1B footnote 'd' change to read:

""For isolates of *H. influenzae* from CSF, only results of testing with ampicillin, **any** of the 3rd-generation cephalosporins **listed** and meropenem are appropriate to report."

WG Vote: 7 – 1- 1 Opposed: didn't want to include ceftazidime to the comment

Subcommittee Vote: Approved to change *H. influenzae* CSF comment as recommended by WG (shown above) Approved 9-1; 1 absent

Note: currently footnote is placed immediately after *H. parainfluenzae*- since it applies to *H. influenzae* it should be moved to appear after *H. influenzae*

– *Haemophilus* spp. - The ad hoc WG recommended moving trimethoprim-sulfamethoxazole from Group A to Group C:

- An E-mail vote of the ad hoc committee was held and were in favor of the move to group C. A motion was made by D. Roe-Carpenter to move forward with the recommendation. The motion was seconded by S. Jenkins **WG Vote: 8 - approved, 0 - opposed, 1 – abstained; the motion Passed**.

Subcommittee Vote: Approved 10-0; 1 absent to move trimethoprim-sulfamethoxazole from Group A to Group C for Haemophilus in Table 1B. Change will also be made in Table 2E Test/Report Group

– *Haemophilus* spp. - Move ciprofloxacin/levofloxacin/moxifloxacin from Group C to Group B and remove gemifloxacin in Table 1B.

- A motion was made by S. Jenkins and seconded by B. Limbago **WG Vote: 8 - approved, 0 - opposed, 1 – abstained; the motion passed**.

Subcommittee Vote: Approved 10-0; 1 absent to move ciprofloxacin, levofloxacin, and moxifloxacin from Group C to Group B and remove gemifloxacin in Table 1B. Corresponding changes will be made in Table 2E as well

– *Haemophilus* spp. - Currently cefuroxime (parenteral) is in Group B and cefuroxime (oral) is in Group C in Table 1B

- Proposal: remove Cefuroxime (parenteral) from Group B and combine it with Cefuroxime (oral) in C, omit words 'parenteral' and 'oral' with changes to corresponding footnote 'e' as follows:

e. Amoxicillin-clavulanate, azithromycin, cefaclor, cefdinir, cefixime, cefpodoxime, cefprozil, cefuroxime, and clarithromycin are ~~oral~~ agents that ~~may be~~ are used as empiric therapy for respiratory tract infections due to *Haemophilus* spp. The results of susceptibility tests with these antimicrobial agents are often not necessary ~~useful~~ for management of individual patients. ~~However, susceptibility testing of *Haemophilus* spp. with these compounds may be appropriate for surveillance or epidemiological studies.~~**WG Vote - 8 - approved, 0 - opposed, 1 – abstained. The motion Passed.**

Subcommittee Vote: Approved 10-0

– *Haemophilus* spp - Other discussions (No votes taken)

- Consider adding tetracycline to footnote E:

  - Tetracycline in Table 1 is specifically as a surrogate for doxycycline
  - Shouldn't doxy be the agent listed for empiric treatment?
  - No motion

- Consider removing aztreonam (gp C) from *H. influenzae* Table 1 - No motion

7. The WG considered a Report from the Intrinsic Resistance ad hoc WG: Dr. Barb Zimmer – Chairholder

- Removal of tetracycline resistance and *Morganella morganii*

  - Reviewed references, discussed concepts of intrinsic resistance (chromosomal and expressed) vs clinical resistance. Be clear on the definition. The ad hoc WG vote was: 10-0-0 to remove tetracycline intrinsic resistance from *M. morganii* in the Table and leave tigecycline. D. Roe-Carpenter made a motion to approve the recommendation form the ad hoc WG. T. Simner seconded the motion. **WG Vote: 9 – approved; 0 – opposed; 0 – abstained. The motion Passed.**

    Subcommittee Vote: Approved 10-0; 1absent to remove 'R' for tetracycline for *Morganella morganii* in Appendix B1.

- MALDI-TOF identification of "new" species and interpretation of AST results
  - Still in discussion stage, the ad hoc WG decided to start working on the organism complexes. Examples: *Enterobacter cloacae* complex, *Acinetobacter baumannii* complex
  - At this point the ad hoc WG was unsure where resultant information will be placed in the documents. One possibility might be a separate taxonomy table at the beginning of the breakpoint table.

    Actions:
    1. Organism complexes were assigned to the ad hoc WG members for study
    2. Will use MALDI-TOF databases to get their complex definitions (US & OUS)
    3. Reviewing any available literature for intrinsic resistance.
    4. Focus primarily on gram-negatives and coagulase-negative staphylococci
    5. The ad hoc WG will get together by March 1 via conference call.

8. Discuss potential addition of a new phenotypic method to screen for carbapenemase production in gram-negative bacteria: Dr. Sanchita Das
   - Carbapenem Inactivation Method
   - Simple and inexpensive:
     400 µL of water with a meropenem disk and add a 10-µL loopful of organisms; incubate for 2 hours. Place meropenem on plate streaked with a susceptible strain of *E. coli.* Incubate for 6 hours. The test result is based upon no zone vs a zone of inhibition
   - Recent publication compared CIM to CarbaNP: CIM was found to be easier to perform and read than the CarbaNP test. Disadvantage: Requires an overnight incubation.
   - NorthShore Validated the test. Modification: Used Tryptic Soy Broth (TSB), and incubated 4 hours vs. 2 hours
   - Used CDC/FDA highly defined isolates for the validation study
   - Easy to perform; extremely cost-effective; up to 8 isolates can be tested on a single Mueller-Hinton agar plate; objective reading

- B. Limbago stated that in her experience they experienced problems with OXA-48 producers; OXA-181 was an issue in the PLOS one publication
- S. Sharp made a motion to move forward with a proposal to conduct a multi-center study validating the performance characteristics of the assay. An expanded study similar to that conducted for the Carba NP assay was recommended.
- 7 sites were included the Carba NP, standard protocol using a standard set of isolates. Multiple disk manufacturers should be evaluated. Reproducibility will also be assessed.
- Interested sites should speak with S. Das.
- Darcie moved the motion forward to create a WG to perform a study equivalent to the Carba NP. S. Jenkins seconded the motion. **WG Vote: 9 – approved; 0 – opposed; 0 – abstained. The motion passed**.

  Subcommittee Vote: Approved further development of disk carbapenemase inhibition assay – 10-0; 1 absent.

9. Discuss the potential need to provide direction when reporting AST results for antimicrobial combinations, particularly when both components exhibit antibacterial activity
   - Identification of the specific problem needs to be better defined
   - How do you report the results?
     Suggestion: If they both increase in concentration proportionately, report both. If one is not increasing and is constant – report the ratio.

   - How do you conduct Quality Control (QC) testing? Is QC testing of both components individually required when both components of the combination exhibit antimicrobial activity?

     Our current example is trimethoprim-sulfamethoxazole as both compounds have activity, but we don't test them individually for QC purposes.
   - We need further discussion on pros and cons as they relate to these issues.
   - S. Jenkins suggested that the issue be tabled and that it be discussed in greater detail on a future conference call.

10. A call for suggestions related to unmet Methods Applications and Interpretations needs was put forth - No suggestions were brought forward at this time.

VIII. REPORT OF THE METHODS DEVELOPMENT AND STANDARDIZATION WORKING GROUP (Electronic Folder 8)

Co-Chairholder – Barbara Zimmer
Co-Chairholder – Dwight Hardy
Recording Secretary – Katherine Sei

Members Present: Bill Brasso, Romney Humphries, Laura Koeth, Ribhi Shawar

1. Standardization of Disk Diffusion methods direct from blood culture.

   Romney Humphries presented the background and proposed protocol to establish guidelines for disk diffusion methods direct from positive blood cultures. Key issues that were discussed included differences between the proposed EUCAST method and proposed CLSI method. EUCAST uses a 1:10 dilution from blood culture, with early reads of the plates at 8 hours whereas proposed CLSI will use 4 drops directly from the positive blood culture broth and the early reads of the plates are 6-8 hours. (It was felt that 8 hours was too prescriptive as the timing would not fit within a normal work shift.) Both methods will also have a standard overnight read of the disk diffusion plates. A preliminary study will be conducted at Accelerate Diagnostics to determine if the manufacturer's broth affects performance, and then a small study will be conducted at 3-5 sites with clinical isolates. The data from the studies will be used to help define the standard method.

2. Atypical Staphylococci

   Romney presented information on the atypical staphylococci isolates that require blood Mueller Hinton Agar (BMHA) for growth. These isolates have multiple colony morphologies, and there are differences between different brands of BMHA in terms of supporting growth or having good zone sizes. These isolates do not always have morphologies that breed true, and they are not solely thymidine auxotrophs. These types of isolates are seen with cystic fibrosis and wound injuries. A study is being conducted to help define the method, which will be presented at the June meeting.

3. Shionogi S-649266

   A new drug S-649266 from Shionogi requires iron depleted cation-adjusted Mueller Hinton broth (ID-CAMHB). Data from Shionogi was presented at teleconferences prior to the CLSI meeting, and the company summarized the data and addressed questions and concerns. This new drug requires Mueller Hinton broth with iron at 0.03 mg/L or less, zinc at 0.5-1.0 mg/L, calcium at 20-25 mg/L, and magnesium 10-12.5 mg/L. The zinc, calcium, and magnesium are added back to the broth after cation depletion. No studies were done to evaluate varying levels of zinc; the zinc level is based on what was present in the broth before cation depletion. Directions were given by Shionogi to accurately read the MICs which include insuring the growth well had >2mm button or pronounced turbidity, and to read the MIC at the first significant drop in growth. The committee asked that clarifying pictures be provided to Text and Tables.

   WG Motion and Vote: Motion from Methods WG: Encourage the sponsor to move forward with a modified version of Proposed Plan 2, using a defined standard for iron concentration in CAMHB 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/recommendations from the Methods WG– Approved 10-0; 1 absent.

4. Harmonization of Disk Mass

Laura Koeth presented the studies to assess if the CLSI and EUCAST disk mass need to be harmonized. Two aspects were considered:

- Does one system result in better performance? Based on the data, it does not appear that one is better than the other.
- Are there other reasons, such as simply the need to have a single disk mass globally? To implement a single disk mass globally would require pharmaceutical companies to do additional studies to validate a change, and there is no source of funding for this kind of endeavor.

> WG Motion: Does the group affirm that the data review doesn't warrant a change in disk mass? 6 in favor, 1 abstention. Motion passed.

The charge of this ad hoc WG is completed.

5. Tedizolid QC and MIC Testing

Laura Koeth presented data, for information only, on the correlation of QC *S. aureus* ATCC® 29213 with an increase in categorical results with clinical isolates going from S to I. The QC range for *S. aureus* ATCC® 29213 is 0.25-1 µg/ml. When 29213 has an MIC of 1 µg/mL when tested in various labs, approximately 25% of the clinical isolates were intermediate. When 29213 had an MIC of 0.5 µg/mL, less than 1% of the clinical isolate results were I. There were questions if this could be attributed to reading trailing differently in labs, reading pinpoint growth as growth, or if this was due to variations in tray setup or tray manufacture. A tier 2 QC study will be conducted by Merck and Bayer, and will include an additional organism - *S. aureus* ATCC® 25923 as well as reading to different endpoint descriptions.

6. Broth Microdilution Ad Hoc Working Group (BMWG)

- The BMWG presented four recommended changes to M7:

1. Add the word "calibrated" to statement in M7, section 3.3.3, step 3 – "Use either a *calibrated* photometric device…." **Approved by Subcommittee 10-0; 1 absent**

2. Add to M7 section 3.9, "If using cover trays, place *one on top of the stack only*." **Approved by Subcommittee 10-0; 1 absent**

3. For describing a valid growth well, add wording, "For a test to be considered valid, acceptable growth (>=2 mm button or definite turbidity, *or growth that is at least comparable to that in the antibiotic containing wells*)."

4. Insert a step to M7, section 3.8.2, "…thaw broth microdilution panels at room temperature up to 2 hours, and then inoculate within 4 hours total".

   These four recommendations were presented to the Development Working Group. Of these recommendations, numbers 1 and 2 were presented to the subcommittee and approved. The remaining two items were sent back to BMWG and the M7 Text Working Group for further wording clarification.

- The BMWG Stats group presented data for information on the following studies conducted with frozen broth microdilution panels:

1. Shelley Miller presented the reproducibility of results for Enterobacteriaceae that were SDD for cefepime. The categorical reproducibility of isolates that were SDD on the first test was ~54% on the second test.
2. Michael Ullery presented data on the variability of results with ceftriaxone with Enterobacteriaceae with replicate testing on the reference panel. The spread for many isolates were greater than 3 doubling dilutions.
3. The text in M7 on page 7 discusses the term "true" MIC, and then points out that, "Even under the best controlled conditions, a dilution test may not yield the same end point each time it is performed."

IX. REPORT OF THE QUALITY CONTROL WORKING GROUP (Electronic Folder 9)

Co-Chairholder –Steve Brown
Co-Chairholder –Sharon Cullen
Recording Secretary – Jim Ross (not voting)

Members Present: Patti Conville, Bob Flamm (not voting, will rotate off WG), Stephen Hawser, Janet Hindler, Michael Huband, Erika Matuschek, Ross Mulder, Susan Munro, Bob Rennie, Mary York
Members Absent: Denise Holliday

Invitation: Seeking new representative to represent pharmaceutical manufacturers

Agenda

1. Propose QC ranges based on M23 Tier 2 Studies for 7 antimicrobial agents and 18 QC ranges:
   - Bis-EDT MIC ranges for *S. aureus* ATCC® 29213, *E. faecalis* ATCC® 29212, *S. pneumoniae* ATCC® 49619, *E. coli* ATCC® 25922, *P. aeruginosa* ATCC® 27853, and *H. influenzae* ATCC® 49247 (files 2 0 and 2 1)
   - Azithromycin disk diffusion ranges for *N. gonorrhoeae* ATCC® 49226 (files 3 0 and 3 1)

- S-649266 disk diffusion ranges for *E. coli* ATCC® 25922 and *P. aeruginosa* ATCC® 27853 (files 4 0 and 4 1)
- Cefepime-tazobactam disk diffusion ranges for *S. aureus* ATCC® 25923, *E. coli* ATCC® 25922, *E. coli* NCTC® 13353, *P. aeruginosa* ATCC® 27853 and *K. pneumoniae* ATCC® 700603 (files 5 1 and 5 5)
- S-649266 MIC ranges for *E. coli* ATCC® 25922 and *P. aeruginosa* ATCC® 27853 using Chelex treated MHB (files 5 2 and 5 5)
- Gepotidacin MIC ranges for *N. gonorrhoeae* ATCC® 49226 using agar dilution (files 5 3 and 5 5)
- Debio 1452 disk diffusion ranges for *S. aureus* ATCC® 25923 (files 5 4 and 5 5)

QC Ranges (see Appendix A at the end of these minutes for all QC reviewed and approved)

2. Tier 3 QC: Review monitoring data and recommend additional actions as appropriate, 15-30 minutes (Erika Matuschek, Sharon Cullen for Denise Holiday) (files 1 2 thru 1 4 and 7 0 thru 7 4)

   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. Tier 3 QC data was reviewed and the following recommendations were made:

   - 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 for those indicated below. Routine disk diffusion data is acceptable; data from frozen reference is needed for MIC (data from commercial MIC devices cannot be used). Pharmaceutical companies/QC study coordinators are also requested to provide the original M23 Tier 2 data where indicated. M23 Tier 3 requirements include 3 labs, 2 media lots, 10 reps/lab and 50 reps per media, 2 disk lots for a total of 500 results for disk diffusion and 250 for MIC.
   - A range change is recommended for disk diffusion with Cefepime and *P. aeruginosa* ATCC® 27883 from 24-30 to 25-31mm – WG Vote 11/0/0/1 and Meropenem disk diffusion with *E. coli* ATCC® 25922 from 28-34 to 28-35 WG Vote 11/0/0/1.

QC Strain (ATCC)	Antimicrobic	Method	Current Range	Action Recmd	Concern	Date Reported
P. aeruginosa 27853	Cefepime	Disk	24-30,	Change to 25-31 WG Vote: 11/0/0/1 **Subcommitte Vote: Approved 10-0; 1 absent**	Out high, variability between labs Tier 3: 13% at 31 (2009-2015, 10 labs, 775 results) Tier 2 control drug for S-649266 and Cefepime/tazobactam: vast majority of results 27-30	NA
E. coli 25922	Cefixime	Disk	23-27	Get original M23, collect additional data	Out low.	NA
E. coli 25922	Meropenem	Disk	28-34	Change to 28-35 WG Vote: 11/0/0/1 **Subcommitte Vote: Approved 10-0; 1 absent**	96% in range including original Tier 2, (larger % out high with current data with several labs). 99% in range with 28-35.	NA
K. pneumoniae 700603	B-lactam/ B-lactamase inhibitors	Disk	No range	Collect data	Alternative for E. coli 35218	NA
E. coli 25922	Ciprofloxacin	Disk	30-40	Collect additional data	Wide range (consider narrower range). Zones often in lower part.	Dec-15
P. aeruginosa 27853	Imipenem	Disk	20-28	Collect additional data	Zones in the lower part or below range reported	Dec-15
N. gonorrhoeae 49226	Doxycycline	Disk	No range	Include in other study to establish range	Submitted by Mary York	Jan- 16

No changes recommended. Additional data requested for assessment.						
QC Strain (ATCC)	**Antimicrobic**	**Method**	**Current Range µg/ml**	**Action Recmd**	**Concern**	**Date Reported**
S. pneumoniae 49619	Cefuroxime	MIC	0.25-1	Request data/feedback	Mode at 0.25	Jun-2013
P. aerug inosa 27853	Ertapenem	MIC	2-8	Monitor	Out low with some labs	NA
E. faecalis 29212	Minocycline	MIC	1–4	Monitor/request feedback	Mode at low end at 16 hrs, bimodal at 18 hrs, at middle of range at 20 hrs	NA
S. aureus 29213	Minocycline	MIC	0.06–0.5	Monitor/request feedback	Mode at low end of current range regardless of read time 16-20 hr	Jun-2013
E. faecalis 29212	Teicoplanin	MIC	0.06-0.25	Monitor	Data in range without tween, some out low with tween. Original data out low with current range.	NA
H. influenzae 49247	Tigecycline	MIC	0.06-0.5	Retain current range	Small number out high	NA
B. fragilis 25285	Pip/tazo	MIC (Agar)	0.12-1	Monitor/request feedback	Out low (control M23 study Jan 2010)	Jun-2013
E. faecalis 29212	Gentamicin	MIC	4-16	Monitor/request feedback	Some out low. Cations, pH in acceptable range (BD)	Jan-2015
E. faecalis 29212	Tobramycin	MIC	8-32	Monitor/request feedback	Some out low. Cations, pH in acceptable range (BD)	Jan-2015

Other Discussions

- Tedizolid MIC testing was discussed at the Methods Working Group which recommended additional testing which can be used to confirm or reassess reading instructions and QC range.
- The potential for disk mass changes was discussed at the Methods Working Group. No QC studies are needed if disk mass is not changed as discussed.
- The QCWG was requested to review and potentially revise the QC organism maintenance flow chart from M07 and M02. Mary York, Janet Hindler and Susan Munroe will review and propose changes in June 2016.
- Janet Hindler and Sharon Cullen will review recommendations for QC testing of combination antimicrobial agents with *E. coli* NCTC 13353, *P. aeruginosa* ATCC® 27853, *K. pneumoniae* ATCC® 700603 for consistency, recommendations for routine or

supplemental testing and any gaps where there are no ranges for the single drug with these QC strains.

- Jim Ross to submit request to ATCC to provide *E. coli* NCTC 13353. This organism is currently available from the UK and at least one US supplier. Availability from ATCC® would provide additional options for shipment within the US.

3. Troubleshooting Guide: Review proposed improvements and identify additional content to consider, 15-30 min (Patricia Conville, Sharon Cullen for Denise Holiday) (files 1 1 and 8 0)

Updates are needed for both Disk and MIC Troubleshooting Guides. Inputs include information from M2 and M7, feedback from AST Subcommittee participants on other improvements and recommendations from Ad Hoc Group for Broth Microdilution. The Troubleshooting Guide provides valuable information to many stakeholders.

The proposed timeline is to get final approval in June 2016. Inputs should be provided to Denise Holiday and Erika M Matuschek for Disk Diffusion and Patricia Conville and Janet Hindler for MIC. Some of the initial inputs include the following. Vote to include all updates to troubleshooting WG vote - 11/0/0/1

Table 5G MIC Troubleshooting Guide: Recommended additions

Antimicrobial Agent	QC Strain	Observation	Probable Cause	Comments/Suggested Actions
Ampicillin Piperacillin Ticarcillin	***E. coli* ATCC® 35218**	**MIC too low**	**Spontaneous loss of the plasmid encoding the β-lactamase gene**	**Retrieve new QC strain from stock; store strain at temperatures at -60°C or below[a]**
Chloramphenicol Clindamycin Erythromycin Linezolid Tetracycline	***S. aureus* ATCC®29213 or *E. faecalis* ATCC®29212**	**MIC too high**	**Trailing endpoint**	**Read at first well where the trailing begins; tiny buttons of growth should be ignored[b]**
Trimethoprim and sulfonamides	**Any**	**MIC too high**	**Antagonists in the media or incorrect concentration of thymidine[c]**	**Read the endpoint at the concentration in which there is ≥80% reduction in growth as compared to the control[2]**
Dalbavancin Oritavancin Televancin	***S. aureus* ATCC®29213 or *E. faecalis* ATCC®29212**	**MIC too high**	**Lack of polysorbate-80 in the media**	**Add 0.002% polysorbate-80 to CAMHB[d]**

[a] M100-S25 Table 5A Footnote c
[b] M07-A10 Section 3.11
[c] M100-S25 Appendix D and Section 3.11
[d] M07-A10 Section 3.6.1

Table 4D Disk Diffusion Troubleshooting Guide: Clarified and separated into individual causes and suggested actions for zones too small.

Antimicrobial Agent	QC Strain	Observation	Probable Cause	Comments/Suggested Actions
Aminoglycosides	**Any**	**Zone too small**	**pH of media too low**	**Acceptable pH range = 7.2–7.4 Avoid CO2 incubation, which lowers pH. Action: Need Clarification when testing atypical Staphylococci.**
β-Lactam group	**Any**	**Zone initially acceptable, but decreases and possibly out of range over time. Add: Colonies appear close to the zone edge.**	**Disk has lost potency**	**Use alternative lot of disks. Check storage conditions and package integrity. Imipenem, clavulanate, and cefaclor are especially labile. (Add meropenem)**
Various	**Various**	**Zone too small**	**Contamination Delete: Use of magnification to read zones**	**Subculture to determine purity and repeat if necessary. Add: If discrete colonies continue to grow within the zone, measure the colony-free inner zone.**
Various	**Various**	**Zone too small**	**Use of magnification to read zones**	**Add: Measure zone edge with visible growth detected with unaided eye.**
Various	**Various**	**Zone too small**	**Uneven growth and non-circular inhibition zones**	**Streak plates more carefully and hold the cotton swab lightly on the agar surface.**

No vote taken by the subcommittee on the proposed changes to the troubleshooting guides. Final changes will be presented at the June meeting.

X. AGENDA SUBMISSIONS FOR 5-7 JUNE 2016 MEETING IN SAN DIEGO, CALIFORNIA

Materials for the June 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 may 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 5-7 June 2016 meeting please:

1) Submit agenda materials electronically as a PDF file **on or before Thursday, 12 May 2016.**

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 Patel, PhD, D(ABMM) (vzp4@cdc.gov), Mel Weinstein, MD, (weinstei@rwjms.rutgers.edu) and Tracy Dooley (tdooley@clsi.org) for review.

XI. ADJOURNMENT - The meeting adjourned at 10:08 a.m. on Tuesday, 12 January 2016.

Respectfully submitted,

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

Appendix A. QC Ranges

Drug Name:	**BisEDT (Microbion)**	**SUBCOMMITTEE VOTE: APPROVED 10-0; 1ABSENT**	
Table 6 information:	**Solvent: DMSO**	**Diluent: DMSO with footnote "n" and maximum concentration of 3200**	
Table 6C information if applicable:	**N/A**	**Preparation: N/A**	**Example: N/A**
Glossary information:	**Class: bismuth thiol**	**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
***S. aureus* 29213**	**0.12 – 1**	**10/0/0/2**	**100**	**0.25**	**4**	**63% @0.5**		**Mode for 2 labs 0.5, Lot A mode 0.5**
***E. faecalis* 29212**	**0.5 – 4**	**7/2/0/3**	**96.7**	**1**	**4**	**47% @ 2**		**Lab modes varied from 0.5, 2, 4 (Lab 5 which was removed). 93.2% in range with all labs. Media Lot A 17.5% out high including Lab 5, 8.6% excluding Lab 5**
***S. pneumoniae* 49619**	**0.12 – 1**	**9/0/0/3**	**100**	**0.5**	**4**	**68% @0.25**		**Lab 1, 6, 7 mode at 0.25, Lab 4 at 1 (removed as outlier) 100% in range with Lab 4 Rangefinder: 0.12 – 2. Considered option 0.25-2.**
***E. coli* 25922**	**0.5 – 4**	**9/0/0/3**	**99.6**	**1**	**4**	**78% @ 2**		**Lab modes between 1 and 2**
***P. aeruginosa* 27853**	**0.5 – 4**	**9/0/0/3**	**99.6**	**1**	**4**	**45% @ 2**		**Media Lot A mode 2.**
***H. influenzae* 49247**	**0.015 – 0.06**	**9/0/0/3**	**100**	**0.03**	**3**	**<10%**		

Additional Information (eg, if to be added to Troubleshooting Guide provide info for this):
Study Coordinator: MicroMyx, Agenda Doc ID QCWG 2.1, Control drug levofloxacin.
Rangefinder same range except where noted. Outliers Lab 5 for *E. faecalis* ATCC 29212 & Lab 4 for *S. pneumoniae* ATCC 49619
Media lot A 1 dilution higher MICs with non fastidious QC organisms.
Some trailing or hazy endpoints were noted with media A but no additional comments or instructions were recommended.

Drug Name:	**Azithromycin**			**SUBCOMMITTEE VOTE: NO VOTE TAKEN – WILL COME BACK IN JUNE**
Table 6 information:	**Solvent: No Change**	**Diluent: No Change**		
Table 6C information if applicable:	**No Change**	**Preparation: No Change**		**Example:**
Glossary information:	**Class: No Change**	**Subclass: No Change**	**Agent Abbreviation: 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
N. gonorrhoeae **ATCC 49226**	**Range TBD**	**11/0/0/1**				**NA**		**Original proposal 29-39, 97.1%. Median 34, 11 mm range** **Lab 1 (median 42) excluded as outlier since Pen disk control out of range.** **All labs 28-41, 95.7% in range. 7 labs (excluding Lab 1 & 5) 29-36** **Another option 30-36 (no results at 29)**

Additional Information (eg, if to be added to Troubleshooting Guide provide info for this):
Requested information to potentially establish range with data presented:
1) feedback on incubation conditions in study specifically CO2,
2) mean for colony counts (since broad range was noted),
3) feedback if there was difficulty in reading zone sizes,
4) calculate % in range for range size options to consider, suggest analysis with Rangefinder to assess range and outliers.
Only 2 media manufacturers tested (so standard note should be applied to range if approved).
Testing conducted by 9 labs. Control drug is penicillin.
Study Coordinator CDC, Agenda Doc ID: QCWG 3.1

Drug Name:	**S-649266 (Shionogi) 30 µg disk**			**SUBCOMMITTEE VOTE: APPROVED 10-0; 1ABSENT**
Table 6 information:	**Solvent: Saline**	**Diluent: Saline**		
Table 6C information if applicable:	**NA**	**Preparation: NA**		**Example:**
Glossary information:	**Class: β-lactam**	**Subclass: Siderophore cephalosporin**	**Agent Abbreviation: TBD**	**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
***E. coli* 25922**	**23 – 31**	**9/0/2/1**	**95.3**	**8**	**9**	**NA**		**Rangefinder 22-32 with 98.7% in range** **Media Lot C median 28, Lot A & B 26** **Lab Medians 26-29** **Also considered 23-32**
***P. aeruginosa* 27853**	~~**19-31**~~ ~~**19-28**~~ ~~**20-30**~~ ~~**No range**~~ **20-30**	**NA** **4/4/2/2** **4/4/2/2** **3/4/3/2** **6/2/3/1**	**95.0** **80.0** **91.3** **NA** **96.4%**	**25**	**13** **10** **11** **NA** **11**	**NA**		**Medians for Lot A 24, Lot B 22, Lot C 29** **Medians for Labs 23-26.** **Approved range based on 7 labs excluding Lab B & D which were higher** **Median for Disks 23-26**

Additional Information (eg, if to be added to Troubleshooting Guide provide info for this):
Excluding medium lot C would not meet M23 Tier 2 guidelines However additional data was provided using additional lots of the same manufacturers of MH agar which gave similar results to the Tier 2 Study.
There was no correlation with the lower/higher colony counts and zone sizes in this study. There were some reports of fuzzy zones but not frequent.
Request to sponsor to provide an update in future to confirm or reassess range with 1) QC data from on-going studies, 2) data with additional media manufacture, 3) assess whether or not additional reading instructions are needed.
Study Coordinator: IHMA, Agenda Doc ID: QCWG 4.1

Drug Name:	Cefepime-tazobactam or WCK 4282 (Wockhardt)		SUBCOMMITTEE VOTE: APPROVED 10-0; 1ABSENT
Table 6 information:	Solvent: Cefepime: phosphate buffer (pH 6.0, 0.1M) Tazobactam: water	Diluent: Cefepime: phosphate buffer (pH 6.0, 0.1M) Tazobactam: water	
Table 6C information if applicable:	NA	Preparation: 30/20-µg disk	Example:
Glossary information:	Class: β-lactam/β-lactamase inhibitor combination	Subclass: NA	Agent Abbreviation: FEP-TAZ 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	24-30	10/0/1/1	99.0	27	7	NA		Range Finder: 23-30 (99.4%)
E. coli ATCC 25922	32-37	10/0/1/1	97.9	34	6	NA		Range Finder 31-38 (99.6%)
E. coli NCTC 13353	27-31	10/0/1/1	96.7	29	5	NA		Range Finder 26-32 (100%)
P. aeruginosa ATCC 27853	27-31	10/0/1/1	97.3	29	5	NA		Range Finder 26-32 (100%)
K. pneumoniae ATCC 700603	25-30	10/0/1/1	99.4	27	6	NA		Range Finder same

Additional Information (eg, if to be added to Troubleshooting Guide provide info for this
Data for Cefepime as a control drug was provided with one lot of disks which provided sufficient data to confirm adequacy of this study but were insufficient to establish a range for *E. coli* ATCC NCTC 13353 and *K. pneumoniae* ATCC 700603.
Request to sponsor for Tier 2 study to establish a QC range for *E. coli* NCTC 13353 and *K. pneumoniae* ATCC 700603 for cefepime alone to be able to confirm integrity of the QC strain's ability to evaluate the tazobactam component. (vote 9/1/1/1). Note: will need to add footnote "d" to Table 4A "g" to Table 5A and address recommendations for which strain should be testing routinely or provided as supplemental information.
Study coordinator: JMI, Agenda Doc ID: QCWG 5.1, Control drugs Cefepime and Piperacillin/tazobactam
NOTE: Cefepime P. aerug QC data at high end of current range which correlates with recent Tier 3 data.

Drug Name:	S-649266, (Shionogi)		SUBCOMMITTEE VOTE: APPROVED 9-1; 1 ABSENT
	Solvent: Saline	Diluent: Saline	
Table 6C information if applicable:	Total Fe: 0.03 mg/L or less Zn2+ 0.5-1.0 mg/L, (10-15 µ M)). Ca and Mg concentrations as described for CAMHB	Method to prepare iron deficient cation adjusted Mueller Hinton broth to be described by methods working group.	Example:
Glossary information:	Class: β-lactam	Subclass: siderophore cephalosporin	Agent Abbreviation:	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
E. coli ATCC 25922	0.06 – 0.5	8/0/2/1	99.7	0.25	4	53% @ 0.12	Iron depleted cation-adjusted Mueller-Hinton broth	Media Lot C mode 0.06. Labs A, D, G mode 0.12 Note: Excluding Media lot C shoulder only 32% at 0.12, mode still 0.25 Alternative range 0.12-0.5
P. aeruginosa ATCC 27853	0.06 – 0.5	8/0/2/1	95.0	0.25	4	89.1 @ 0.12	Iron depleted cation-adjusted Mueller-Hinton broth	Media (4 lots tested), Lot modes: C 0.06, A&B 0.12, D 0.25. Lab modes: 0.12-0.25 If Lot C excluded: shoulder 72% @ 0.12, mode still 0.25

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study Coordinator: JMI, Agenda Doc ID: QCWG 5.2, Control drug: Cefepime
4 media lots included. Only one lot of chelex used.
Discussion comments: Lot C was obtained as CAMHB but there is no evidence this contributed to the different results obtained with this lot. After treatment to remove iron, iron and magnesium were measured and were below detectable limits, Ca was above detectable limits prior to adjustment. There was no correlation of the lower colony counts and MIC results.
Request to sponsor: Provide an update in future on QC results from on-going studies to confirm or reassess range.
Note: While there weren't reading issues with the QC strains, trailing is observed with Acinetobacter spp. and the methods WG has approved addition of instructions for reading all organisms with this antimicrobial agent.
Note: Do not publish previously approved ranges with CAMHB

Drug Name:	**Gepotidacin or GSK2140944 (GlaxoSmithKline)**		**SUBCOMMITTEE VOTE: APPROVED 10-0; 1ABSENT**	
Table 6 information:	**Solvent: DMSO**	**Diluent: Water**		
Table 6C information if applicable:	**NA**	**Preparation: NA**		**Example:**
Glossary information:	**Class: Triazaacenapthylene**	**Subclass: NA**	**Agent Abbreviation: GEP**	**Route of Administration: PO, 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
N. gonorrhoeae **ATCC 49226 (agar dilution)**	**0.25 – 1**	**11/0/0/1**	**100**	**0.5**	**3**	**11%@ 0.25**		**Range Finder same**

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study Coordinator: JMI, Agenda Doc ID: QCWG 5.3, Control drug ciprofloxacin
Pronounced Gep-O-tI-da-cin

Drug Name:	Debio 1452 (Debiopharm)		SUBCOMMITTEE VOTE: APPROVED 10-0; 1ABSENT	
Table 6 information:	Solvent: DMSO	Diluent: DMSO footnote "n" with a max concentration of 3200		
Table 6C information if applicable:	NA	Preparation: 5-µg disk		Example:
Glossary information:	Class: FabI inhibitor	Subclass: NA	Agent Abbreviation: FAB	Route of Administration: PO, 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	30-36 mm	9/1/1/1	96.3	33	7	NA	Range established with single manufacturer of disks	Range Finder 29-37 (100%, 9 mm range) Medians: media 32-34, labs 31-35

Additional Information (eg if to be added to Troubleshooting Guide provide info for this):
Study Coordinator: JMI, Agenda Doc ID: QCWG 5.3. Control drug rifampin.
Only one disk manufacturer included.
There were no reading issues noted.