The information contained in these minutes represents a summary of the discussions from a CLSI committee meeting, and do not represent approved current or future CLSI document content. These summary minutes and their content are considered property of and proprietary to CLSI, and as such, are not to be quoted, reproduced, or referenced without the expressed permission of CLSI. Thank you for your cooperation

Summary Minutes
Subcommittee on Antimicrobial Susceptibility Testing
Hyatt Regency San Antonio Riverwalk
San Antonio, Texas
12-13 January 2014

A meeting of the CLSI Subcommittee on Antimicrobial Susceptibility Testing was held on 12-13 January 2014, at the Hyatt Regency San Antonio Riverwalk, San Antonio, Texas. The following were in attendance:

Jean B. Patel, PhD, D(ABMM) **Chairholder**	**Centers for Disease Control and Prevention**
Franklin R. Cockerill, III, MD **Vice-Chairholder**	**Mayo Clinic**
Richard B. Thomson, Jr., PhD, D(ABMM), FAAM **Consensus Committee on Microbiology** **Chairholder**	**Evanston Hospital, NorthShore University HealthSystem**
John H. Rex, MD, FACP **Consensus Committee on Microbiology** **Vice-Chairholder**	**AstraZeneca Pharmaceuticals**

Members Present

George M. Eliopoulos, MD	Beth Israel Deaconess Medical Center
Janet A. Hindler, MCLS, MT(ASCP)	UCLA Medical Center
Stephen G. Jenkins, PhD, D(ABMM),F(AAM)	New York Presbyterian Hospital
James S. Lewis, II, PharmD	Oregon Health & Science University
Brandi Limbago, PhD	Centers for Disease Control and Prevention
Linda A. Miller, PhD	GlaxoSmithKline
David P. Nicolau, PharmD, FCCP, FIDSA	Hartford Hospital
Mair Powell, MD, FRCP, FRCPath	MHRA
John Turnidge, MD	SA Pathology
Melvin P. Weinstein, MD	Robert Wood Johnson Medical School
Barbara L. Zimmer, PhD	Siemens Healthcare Diagnostics Inc.

Advisors Present

Jeff Alder, PhD	Bayer HealthCare
William B. Brasso	BD Diagnostic Systems
Karen Bush, PhD	Indiana University

Michael N. Dudley, PharmD,FIDSA*	The Medicines Company
Marcelo F. Galas	National Institute of Infections Diseases, Ministry of Health, Argentina
Dwight J. Hardy, PhD	University of Rochester Medical Center
Romney M. Humphries, PhD, D(ABMM)	UCLA David Geffen School of Medicine
Gunnar Kahlmeter, MD, PhD	ESMID
Tony Mazzulli, MD, FRCPC, FACP	Mt. Sinai Hospital
Melissa B. Miller, Ph.D., D(ABMM)	UNC School of Medicine
Sumathi Nambiar, MD, MPH	FDA/CDER
Robin Patel, MD	Mayo Clinic
Sandra S. Richter, MD, D(ABMM)	Cleveland Clinic
Helio S. Sader, MD, PhD	JMI Laboratories
Michael Satlin, MD, MS	Weill Cornell Medical College/ NewYork-Presbyterian Hospital
Paul C. Schreckenberger, PhD, D(ABMM), F(AAM)	Loyola University Medical Center
Audrey N. Schuetz, MD, MPH, D(ABMM)	Weill Cornell Medical College/ NewYork-Presbyterian Hospital
Susan Sharp, PhD, D(ABMM)	ASM Representative from Kaiser Permanente-NW
Ribhi M. Shawar, PhD, D(ABMM)	FDA Ctr. for Devices/Rad. Health (CDRH)
Kerry Snow, MS, MT(ASCP)	FDA/CDER
Maria M. Traczewski, BS, MT(ASCP)	The Clinical Microbiology Institute
Hui Wang, PhD	Peking University People's Hospital

* Present for 12 January WG Sessions Only

Reviewers Present

Paul G. Ambrose, PharmD, FIDSA	ICPD/Ordway Research
Robert E. Badal	International Health Management Associates Inc.
Donald Biek, PhD	Cerexa, Inc.
Steven D. Brown, Ph, ABMM	
Diane M. Citron, M(ASCP)	R.M. Alden Research Laboratory
Michael J. Dowzicky	Pfizer, Inc.
German Esparza, BSc	Hospital Santa Clara
Gina L. Ewald-Saldana, CLS(CA), MT(ASCP)	Siemens Healthcare Diagnostics Inc.
Robert K. Flamm, PhD	JMI Laboratories
Thomas R. Fritsche, MD, PhD	Marshfield Clinic
Meredith Hackel	International Health Management Associates, Inc.
Nilda V. Jacobus	Tufts Medical Center
Jack L. Johnson	International Health Management Associates, Inc.

James H Jorgenson, PhD	University of Texas Health Science Center
Scott B. Killian	Thermo Fisher Scientific
Cynthia C. Knapp, MS	Thermo Fisher Scientific
Laura M. Koeth, MT(ASCP)	Laboratory Specialists, Inc.
Sara Blaine Leppanen	Blaine Healthcare Associates
Xian-Zhi Li	Heath Canada Veterinary Drugs Directorate
Dyan Luper, BS, MT(ASCP)SM	BD Diagnostic Systems
Linda M. Mann, PhD, D(ABMM)	Siemens Healthcare Diagnostics Inc.
Maureen Mansfield	Thermo Fisher Scientific
Amy J. Mathers, MD	Univ. of Virginia School of Medicine
Susan D. Munro, MT(ASCP)	
Susan O'Rourke	BD Diagnostic Systems
Elizabeth Palavecino, MD	Wake Forest Univ. Baptist Medical Center
Samir Patel, PhD, FCCM	Public Health Ontario
L. Barth Reller, MD	Duke University Medical Center
Darcie E. Roe-Carpenter, PhD, CIC, CEM	Siemens Healthcare Diagnostics Inc.
Flavia Rossi, MD	University of Sao Paulo
Dale A. Schwab, PhD, D(ABMM)	Quest Diagnostics, Nichols Institute
Katherine Sei	Siemens Healthcare Diagnostics
Sharon Shinn	Siemens Healthcare Diagnostics Inc.
Dee Shortridcge, PhD	bioMerieux
Robert Skov, MD	Statens Serum Institut
Judith N. Steenbergen, PhD	Cubist Pharmaceuticals, Inc.
Gregory G. Stone	AstraZeneca Pharmaceuticals
Jana M. Swenson, MMSc	
Nancy Watz	Stanford Hospital and Clinics
Mary K. York, PhD, ABMM	MKY Microbiology Consulting

Observers Present

April Abbott	University of Washington
Francis Ahern	The Medicines Company
Vanessa Allen, MD,MPH	Public Health Ontario
Pete Bantock	Accelerated Diagnostics
Adam Belley	The Medicines Company
Lynette Y. Berkeley, PhD	FDA CDER
Paul Bien, MS	Cubist Pharmaceuticals
Johanne Blais, PhD	Novartis Institutes for Biomedical Research
Halsey Boyd	Siemens Healthcare Diagnostics
Lynn Boyer	Siemens Healthcare Diagnostics
Carey-Ann Burnham, PhD, D(ABMM)	Washington University School of Medicine
Kathy Burtner	Siemens Healthcare Diagnostics
Sysan Butler-Wu	University of Washington
Mariana Castanheira, PhD	JMI Laboratories
Travis Cooper	Forest Research Institute
Katie Coyle	Becton Dickinson

Scott Cunningham	Mayo
Manel Djiar	bioMerieux
Chris Doern	VCU
Evelyn Ellis-Grosse, PhD	E2g Consulting
Sheila Farnham	bioMerieux
Steve Fitzsimmons, MS, MT(ASCP)	bioMerieux
Barb Gancarz	bioMerieux
Andrea Gough	Thermo Fisher Scientific
Elizabeth Hand	UTHSCSA University Hospital
Henry S. Heine, PhD	Institute of Therapeutic Innovation
Daryl J. Hoban	International Health Management Associates, Inc.
David Howson	Accelr8 Technology Corp
Yoshikazu Ishii	Toho University
Seong Jang, PhD	Food and Drug Administration
Jocelyn Jennings	bioMerieux
Kristie Johnson	University of Maryland
Tiffany Keepers	Cerexa, Inc
Susan Kircher, MS, MT (ASCP)	BD Diagnostic
Roberta Knefel	bioMerieux
Jennifer Lorbach	Thermo Fisher Scientific
Kathryn Lupoli	CDC
Erika Matuschek, PhD	EUCAST
Sally Maysent	Thermo Fisher Scientific
Maureen Mende	Siemens Healthcare Diagnostics
Steve Michalik	bioMerieux
Hiroshige Mikamo, MD, PhD	Aichi Medical University Graduate School of Medicine
Shelley Miller	UCLA
Lori T. Moon, MT(ASCP)	MSU Diagnostic Center for Population & Animal Health
Ian Morrissey, MBA, PhD, FRSM	IHMA Europe Sàr
Ross Mulder	bioMerieux
Sean Nguyen	Children's Medical Center
Jennifer O'Connor	Siemens Healthcare Diagnostics
Ryan Owen, PhD	FDA
Chris Pillar	Micromyx
Shannon Popson	Siemens Healthcare Diagnostics
Denise Robinson	OU Medical Center
Nilia Robles-Hernandez	bioMerieux
Carole Shubert	bioMerieux
Jennifer Smart	Theravance Inc.
Janine Spafford	BD Diagnostic Systems
Debora Sweeney	Micromyx, LLC
Kazuhiro Tateda, MD, PhD	Toho University School of Medicine
Joyce Tjhio	

Susan Thomson	Mast International
Grace M. Thorne, PhD	Cubist Pharmaceutaicals
Ben Turng	BD Diagnostic Systems
Kenneth Van Horn, PhD, D(ABMM)	Focus Diagnostics
Dr. Peter Warn	Euprotec Ltd
Collette Wehr	Siemens Healthcare Diagnostics

CLSI Staff

Tracy A. Dooley, BS, MLT (ASCP)
Erica Berlanger
Glen Fine, MS, MBA, CAE
Marcy Hackenbrack, MCM, M(ASCP)
Luann Ochs, MS

TABLE OF CONTENTS

I. MEETING/OPENING REMARKS

Dr. Jean Patel called the meeting to order at 8:00 a.m. on Monday, 13 January 2014. This meeting has a shorter plenary session schedule (one day vs the normal two day plenary) due to all the work and decisions made at the June 2013 meeting that has since been published. There is still a lot of on-going work being done outside of the January and June meetings including revisions of documents M45 and M23 as well as various topics being addressed by the standing working groups (WGs) and various ad hoc WGs. 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.

Dr. Patel discussed the recent changes to the subcommittee including the addition of 2 new voting members: Brandi Limbago from CDC and David Nicolau from Hartford Hospital. New advisors include:

- Bill Brasso from BD Diagnostics representing the Susceptibility Testing Manufacturers Association (STMA)
- Marcelo Galas from National Institute of Infectious Diseases, Ministry of Health, Argentina
- Tony Mazzulli from Mt. Sinai Hospital
- Cathy Petti
- Helio Sader from JMI Laboratories
- Michael Satlin from Weill Cornell Medical College
- Paul Schreckenberger from Loyola University Medical Center
- Maria Traczewski from The Clinical Microbiology Institute

Other rotations/changes:

- Members who rotated to advisors: Jeff Alder and Dwight Hardy

- Advisors who rotated to reviewers: Steve Brown, Ed Cox, Cynthia Fowler, Harriette Nadler, Flavia Rossi, Jana Swenson, and Joe Toerner.

- Retired: Bill Craig

Dr. Patel also addressed some business items including:

- Communications - whenever e-mails are sent to Dr. Patel she requested that Ms. Dooley is copied so that she is aware and can follow-up if necessary.

- New Subcommittee Structure – over the past year the subcommittee has created a new working structure of standing WGs with smaller ad hoc WGs reporting to them. This allows the oversight standing WG to review issues that may need to be addressed and then assign an ad hoc WG to take on the work. Dr. Patel asked if anyone has suggestions to assist in making this new structure more efficient, please let her know. One suggestion that Dr. Patel received regarding the standing WGs was to provide guidance on how these WGs can efficiently work with the ad hoc WGs that report to them.

II. CLSI UPDATE

Ms. Luann Ochs, Senior Vice President of Operations with CLSI welcomed everyone to the meeting and gave an overview of some of the updates within CLSI including:

- New Voting Process – The CLSI consensus voting process has been changed from four levels of voting to two levels of voting to help reduce the time it takes to publish a document without affecting the quality. This would not apply to supplements like M100 but would to other documents produced by the subcommittee such as M02 and M07.

- Version 2 of the electronic eM100 was released on 10 January. This is an electronic version of M100 that is a searchable, easy to use, interative database that allows users to customize searches specific for their formulary. There are various pricing levels, allowing it to be affordable to labs. There is a free 30-day trial so that users can try eM100 and see the various features for those that are interested in learning more about this product.

- Development CLSI Communities of Interest – microbiology is one of the 5 communities that is expected to go live on the CLSI website at the end of the month and will include articles, case studies, blogs, chat rooms, "ask the expert" and links to other microbiology related websites. Please take a look and join the conversation!

Ms. Ochs then introduced CLSI staff present at the meeting as follows:

- Mr. Glen Fine, Executive Vice President;
- Tracy Dooley – Senior Project Manager and Staff Liaison to the Consensus Committee on Microbiology and Consensus Committee on Molecular Methods;
- Marcy Hackenbrack – Project Manager for various projects under Microbiology as well as Molecular Methods and Quality Systems and Laboratory Practices; and
- Erica Berlanger – Meeting Manager who coordinates all the logistics for these meetings.

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. Karen Bush and Dr. George Eliopoulos provided updates that will be added to the summary.

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

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

Members Present: Seth Housman, Romney Humphries, Laura Koeth, Sandra Richter, Darcie Roe-Carpenter, Katherine Sei, Susan Sharp, Ribhi Shawar, John Turnidge, and Mel Weinstein

1. Report from Anaerobe Ad Hoc Working Group: establishing breakpoints and selecting methods for testing vancomycin against gram-positive anaerobes – Chairholder: Dr. Darcie Roe-Carpenter
Members - Audrey Schuetz, Joanne-Dzink-Fox, Nilda Jacobus, Hanna Wexler, Diane Citron, Steve Jenkins, Laura Koeth, Karen (Kitty) Anderson, Cindy Knapp, Meredith Hackel

   a. Continuing to examine data for broth microdilution testing of anaerobes other than *Bacteroides fragilis* group members. Will re-examine data at genus and/or group level if susceptibility patterns are similar for various species, to increase denominators for analysis purposes.

   b. To assess whether interpretive criteria require revision to be make them more in line with those for aerobes, and for anaerobes when using EUCAST breakpoints, the group is requesting assistance from an individual with considerable experience in PK/PD issues (eg, a PharmD with that skill set).

   c. With a goal of developing Epidemiological cut-off values when testing gram-positive anaerobes for susceptibility to vancomycin, appropriate verbiage will be developed to explain usage of such interpretive criteria in a clinical breakpoint table for the next AST Subcommittee (SC) meeting.

   d. Updating Appendix D – updating with susceptibility data from 2010 – 2011 – 2012 – 2013; Present data at next meeting

   e. Table 2J – General Comments – Comment changed to: The "intermediate" category includes isolates with antimicrobial agents MICs that approach usually attainable blood and tissue levels, and for which response rates may be lower than for susceptible isolates. The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated (e.g., quinolones and β-lactams in urine) or when a higher than normal dosage of a drug can be used (e.g., β-lactams). This category also includes a buffer zone, which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

      Refer to Figure 2 in the M11-A8 for examples of reading endpoints. To achieve the best possible levels of a drug in abscesses and/or poorly perfused tissues, which are encountered commonly in these infections, maximum dosages are used along with appropriate ancillary therapy, it is believed that organisms with MICs in the susceptible range are generally amenable to therapy, and those with MICs in the intermediate range may respond, but patient response should be carefully monitored. Ancillary therapy, such as drainage procedures and debridement, are of great importance for proper management of anaerobic infections.

f. Table 1C – Note 2 – Comment reduced to: If susceptibility testing is requested in a polymicrobial infection, the most resistant strain must be considered first and reported (e.g., *Bacteroides fragilis* group).

g. Table 1C – Note 3 – Comment reduced to: Some *Clostridium* species (eg, *C. perfringens, C. septicum,* and *C. sordellii*) may be the singular cause of an infection, are typically susceptible to penicillin and ampicillin, and should be tested and antimicrobial susceptibility testing results reported.

2. Informational presentation: Broth Microdilution (BMD) Ad Hoc Working Group – Chairholder: Mr. Bill Brasso

Members - Susan Kircher, Cindy Knapp, Laura Koeth, Katherine Sei, Ribhi Shawar, John Turnidge, Michael Ullery

a. Preliminary goals defined by the ad hoc WG included the following:

- Identify **critical variables** and the **common sources of variability** inherent in the broth microdilution method.
- Determine how these affect the reproducibility of MIC results.
- Make recommendations to improve upon them.
- Establish an acceptable level of variability in this reference method that can be factored into the acceptance criteria.
- Publish these findings, if appropriate, in the CLSI M7, M52, M100 and other documents that address the Broth Microdilution method.

b. Discussions ensued as to what are the critical variables and the common sources of variability inherent in BMD method. The following were raised:

- 5 main categories – the antimicrobial **agent**, the **organism**, the **medium**, the **growth conditions**, and the **reading method.**
- Also - the **readers**, and the intra- and inter-lab **variability** must be taken into account.
- Inter-lab variability, different laboratories getting different results, may be the most critical.
- Decisions based on data from a single laboratory are therefore ‘not representative of the whole’.
- The thought was to employ M23-like studies to control these as much as possible.

c. How these various issues impact result reproducibility was also addressed.

- It was proposed that the team start with Quality Control organisms and on-scale data, and then expand to larger populations; challenge sets, etc.

- Whether retrospective studies or new testing would be required for these analyses was also discussed.

d. At this point the plan is to focus just on BMD and not to expand efforts to disk diffusion testing at this time, but possibly in the future.

e. The group expressed the need to work with the M23 group to address issues including Quality Control (QC) data.

f. QC data for cefazolin are being examined because most laboratories test this compound routinely and the breakpoints were recently changed.

g. Other issues raised included potential confounding factors such as the methods by which testing panels are prepared, trailing endpoints, adherence to standard methods, eg, media pH, need for CO_2 for growth with some species, etc, and the fact that variables may be organism/antimicrobial agent (bug/drug) specific.

h. The possibility of including photographs of specific bug/drug issued was raised.

i. Collaborating and/or consulting with the M23 WG were also proposed.

j. The plan going forward is to present this information to the full Methods WG at the June meeting, targeting areas in the method where reducing the variability can significantly improve intra- and inter-laboratory performance.

3. Report from the Polymyxins Ad Hoc Working Group: Methods for AST of Polymyxins – Co-Chairholders - Dr. John Turnidge and Dr. Johan Mouton

Members – Steve Jenkins, Roger Nation, Alasdair MacGowan, Luis Martinez-Martinez

a. The results of testing in Teflon-coated mini-muffin pans as initially described by Katherine Sei were discussed.

b. Results suggested that in addition to possibly decreasing the sticking of polymyxins to surfaces, polysorbate may, in fact, have some type of synergistic activity with the polymyxins against gram-negative bacilli. This effect was not observable against organisms for which the MICs were higher.

c. The question was raised as to whether “persisters” may remain both in vitro and in vivo following exposure of some gram-negatives to the polymyxins.

d. It was pointed out that the polysorbate issue was originally brought to the CLSI because of perceived problems with QC testing.

e. It was also pointed out that *E. coli* ATCC® 25922 is not a very useful organism for QC testing and that a new QC strain is probably needed.

f. Discussions ensued indicating that the stick of polymyxins to surfaces in test systems is somewhat saturable at lower levels (0.3 – 0.5 µg/mL may be lost) and may impact the results of MIC testing for more susceptible organisms when the MICs are < 1 µg/mL.

g. The WG voted 8/1/1 to recommend to the full AST SC that polysorbate not be routinely included in test systems for the polymyxins.

Subcommittee vote:

Motion – A motion was made and seconded to not include polysorbate-80 in the testing method as recommended by the WG. Approved 11-0; 1 absent.

To be consistent with this decision, QC ranges for Colistin and Polymyxin B tested with 0.002% polysorbate 80 will be deleted from Table 5A in M100.

h. A proposal was also made to look for a new QC organism for the testing of these compounds.

i. It was also suggested that a comment may be needed indicating that MIC results < 1 µg/mL may not be meaningful.

j. It was further suggested that the impact of sticking may need to be evaluated for the various plastic matrices used in MIC test systems.

4. Informational presentation: CarbaNP Ad Hoc Working Group – Co-Chairholders - Dr. Robin Patel and Maria Traczewski

Members: Brandi Limbago, Scott Cunningham, Audrey Schuetz, Stephen Jenkins, Romney Humphries, Elizabeth Palavecino

k. Some of the potential advantages of this approach for carbapenemase detection were discussed including its improved specificity over the modified Hodge test and the fact that it shortened turnaround time as it is a 2 hour assay.

l. Results of a study conducted at the Mayo Clinic were discussed indicating that the test performed quite well overall with 100% specificity, but that a few carbapenemase producing strains of *Pseudomonas aeruginosa* were missed as were organisms producing an an OXA-48 like enzyme, a VIM-2, and a SME-2.

m. The possibility of using a combined lysis step in the assay was discussed.

n. In a possible multicenter study of the method, the suggestion was made to include a few *Proteus* spp. for which the carbapenem MICs are somewhat elevated.

o. The fact was made that this method may be difficult for many clinical laboratories to conduct in that plates or tubes would need to be prepared on site.

p. The question was posed as to whether the assay might be modified and performed in some disk format. A recommendation was made to investigate this possibility as it might facilitate such testing in clinical laboratories.

q. The panel of challenge organisms expressing specific resistance mechanisms suggested for inclusion in the proposed multi-center study were the following:
   - KPCs
   - NDMs
   - SMEs
   - VIMs
   - IMPs
   - OXA-48s (and possibly other OXA enzymes)
   - ampC hyper-producers with porin mutations
   - carbapenem-susceptible ampC producers

r. The WG voted 9/0/1 to recommend to the full AST SC that the Carba-NP project be moved forward and that the proposed multi-center study be conducted to further evaluate the value of this methodology for clinical labs.

5. Update from the Intrinsic Resistance Ad Hoc Working Group – Chairholder: Dr. Barbara Zimmer

Members - Dyan Luper (Recording Secretary), Jeff Alder, Rafael Canton, German Esparza, Kate Murfitt, Sandy Richter, Susan Sharp, Carole Shubert, Paul Schreckenberger, Tom Thomson

a. A question was raised related to the aminoglycosides and *Serratia marcescens*. The impact on laboratories that employ cascade reporting was raised as a concern.

b. Some thought that the Table may not be the best place for this and that it may be better addressed by the Text and Tables WG.

c. Discussions also took place regarding the reporting of tetracycline for strains of *Serratia marcescens*. The WG voted 5/2 to add a footnote indicating that these organisms are innately resistant to the tetracyclines, but to exclude tigecycline because of insufficient information.

After discussions with the SC, the WG will review additional data and come back with a recommendation.

6. The Methodology WG discussed the potential need for a definition of a "surrogate antibiotic". As we consider including additional surrogate compounds for use in testing, the WG asked:

   a. "What exactly IS a surrogate?" Historical research has not been particularly helpful in addressing this question.

      - How does a surrogate differ from a screen? Note: A definition for a 'Screen' test currently exists in M100.
      - Is it the 'or' described in M100 instructions?
      - Some felt that the term was applicable if other agents CAN'T be tested, or if they WON'T be tested.
      - Some felt that they are primarily for screening purposes.
      - Others felt that they were primarily used when related drugs are not available for testing.

   b. Another opinion rendered was that they allow laboratories to limit the number of antibiotics tested when the activities of certain compounds are very similar.

   c. The question was raised as to the availability of clinical outcomes data when "surrogate" testing is employed.

   d. Discussion ensued related to Table 1 and inclusion of antibiotics in the same box with or without an "or". Currently there is a description in M100 for "or" as follows:

      - Drugs listed in single box have similar SIR and clinical efficacy;
      - cross-resistance/-susceptibility data complete;
      - results from one can be used to predict the other
      - ≥100 Resistant strains were tested with 95% agreement
      - Without an 'or' one must test each agent directly

   The SC agreed that an ad hoc WG will be formed to review/address:

      - Tables 1 and 2 (particularly the *Enterobacteriaceae* and the *Stenotrophomonas*) and recommend the deletion of drugs from Tables 1 and corresponding Table 2 that are no longer available.
      - Review antimicrobial agents in these tables and determine which ones are not considered appropriate to treat the organisms listed.

      - Address discussion points from Intrinsic Resistance WG including:

         - Aminoglycoside rules, with cascade reporting as well as antibiotic stewardship. If gentamycin is S, many do not report out tobramycin or amikacin, even if they are

R. In addition, it was mentioned that some hospitals also cycle through their aminoglycosides. A lot only want 1 aminoglycoside reported.

- Tables 1 and 2 – particularly the *Acinetobacter* vs. the third generation cephalosporins and *S. maltophilia* vs. ceftazidime. For *S. maltophilia*, the IR WG felt the references indicated that it was R. But there are breakpoints. For *Acinetobacter* – EUCAST calls the third generation cephalosporins IR, but the IR WG felt that there were references to indicate that they were not intrinsically resistant (the IR WG thinks the latter is fairly important with newer species being isolated from what is formerly the *A. baumannii* complex.

e. A motion was made by the WG to review the relevant documents and list tests that are referred to as screens versus surrogates and re-evaluate the findings at the next meeting. The WG vote was 9/0/1 to take this tack. John Turnidge agreed to take this initial effort on as a project.

f. The WG agreed that we should seek guidance from the full AST SC as to:

- Whether we should work to develop a definition and criteria for 'surrogate', or is it covered by 'or'?
- Whether we need to clarify if surrogates should not be tested for their own use, but rather as "stand-ins" (e.g., cefoxitin, pefloxacin)?
- Whether 'Surrogate' implies that direct testing of therapeutic agent is less reliable?
- Whether a revision of the definition of a 'screening test' is required?, and
- Whether or not additional testing is required when one uses a "surrogate" antibiotic?

The SC agreed that it would be helpful to see how the terms 'surrogate' vs 'screen' is used in documents and then determine if surrogate should be defined.

7. **** Request for Information**: Historic criteria used to establish testing surrogates.
8. **** Request to the SC for Isolates**: Atypical strains of *Staphylococcus aureus* that fail to grow in usually employed MIC panels and thus require alternate testing methods. Romney Humphries agreed to accept and collect such isolates for a potential future laboratory study on this issue, possibly using Mueller-Hinton agar with blood as a medium.
9. Call for unmet Methods needs.

V. REPORT OF THE SDD AD HOC WORKING GROUP (Electronic Folder 6)

Co-Chairholders - Dr. Jim Jorgensen and Dr. Mel Weinstein
Members: Bill Brasso, Mike Dudley, George Eliopoulos, Susie Sharpe

Charge of the WG (Phase 1):

- Develop general guidelines for when the SDD interpretive criterion would be considered.
- Identify and prioritize existing breakpoints which need review for potential application of SDD.

The WG held 2 conferences calls during which time they discussed/reviewed the following:

- Who will be impacted and who will understand SDD
- Concerns about readiness to implement with cefepime
- Readiness for implementation of cefepime in January, 2014
- Reviewed language for SDD
- Decided that only doses included in the FDA-approved drug labels should be used
- Decided that Monte Carlos would be needed to assign SDD doses and MICs
- Reviewed table of β-lactam breakpoints, doses used to set S breakpoints, possible SDD higher doses
- Decided SDD would not apply to penicillins, carbapenems, cefazolin, ceftaroline, cefuroxime
- Candidates: cefotaxime, ceftriaxone, cefoxitin, ceftazidime, ceftizoxime, aztreonam

The initial charges of the WG were completed and the group disbanded.

Phase 2 Gather Data:

Co-Chairholders - Dr. Jim Jorgensen and Dr. Mel Weinstein
Members: Paul Ambrose, Mike Dudley, George Eliopoulos, Jim Lewis, Helio Sader, John Turnidge

Data reviewed:

- Monte Carlos for the 6 drugs presented in June 2004
- Possible SDD Doses and MICs based on current I:
  - Cefotaxime – 2 g q 8h for 2 µg/mL
  - Ceftriaxone – 2 g q24h for 2 µg/mL
  - Ceftazidime - 2 g q 6h for 8 µg/mL
  - Ceftizoxime – 2 g q 8h for 2 µg/mL
  - Aztreonam – 2 g q 6h for 8 µg/mL
  - Cefoxitin possibly 3 g q 6h for 16 µg/mL?
    - Possibly lower S breakpoint and lower S dose (similar to cefuroxime)

Cefoxitin and Cefuroxime

- S breakpoints set using high doses
- Cefoxitin
  - S ≤8 µg/mL based on 2 g q 6h for "moderately severe or severe infection"
  - Higher does are 2 g q 4h or 3 g q 6h
  - "uncomplicated" – 1.5 g q 6-8h

- Cefuroxime
  - S ≤8 µg/mL based on 1.5 g q 8h for "severe or complicated infection"
  - 3 g q 8h for meningitis
  - "uncomplicated" 750 mg q 8h

Next Steps/Suggestions Disussed at the Working Group Session:

- Look at doses most frequently used in the U.S. (data is available thru the CDC)
- Look at possibly going off FDA-approved label doses and look at those doses frequently used
- Consider other drug classes down the line

VI. M45 WORKING GROUP UPDATE

Co-Chairholder – Dr. Sandra Richter
Co-Chairholder – Ms. Janet Hindler

Working Group Members: Kathy Bernard, Mariana Castanheira, Diane Citron, Marc Couturier, Tom Fritsche, Romney Humphries, Jim Jorgensen, Scott Killian, Peggy Kohner, Erika Matuschek, Samir Patel; Advisor: Pat McDermott

Dr. Richter gave an overview of the updates that the M45 WG are working on as they revise the Document. Some of the issues that they are addressing include:

- *Aeromonas* spp. and *Plesiomonas shigelloides*
  - harmonization of the β-lactam breakpoints (*Enterobacteriaceae* or *Pseudomonas*)
  - assessment of fluoroquinolone breakpoints

- *Bacillus* spp. (except *B. anthracis*)
  - addition of meropenem breakpoints
  - new genera (*Brevibacillus*, *Lysinibacillus*, *Paenibacillus*)

- *Campylobacter jejuni*/*coli*
  - medium issues; one set of incubation conditions
  - susceptible disk breakpoints for ciprofloxacin and erythromycin (currently resistant breakpoints only)

- Coryneform bacilli
  - taxonomy issues (*Trueperella*)
  - penicillin breakpoints
  - the EUCAST disk diffusion procedure with MHF media (MHA with 5% horse blood and 20mg/L NAD)

- HACEK - the problem of growth failures

- *Helicobacter pylori*

  - fluoroquinolones, amoxicillin, metronidazole, and tetracycline breakpoints
  - possible comment regarding macrolide resistance

- *Lactobacillus* spp. - meropenem breakpoints

- *Vibrio* spp. - harmonization of β-lactam breakpoints (*Enterobacteriaceae* or *Pseudomonas*)

- Review of QC tables for consistency with M100

- Addition of new tables for
  - *Aerococcus* spp.
  - *Gemella* spp.
  - *Lactococcus* spp.
  - *Micrococcus* spp.
  - *Rothia mucilaginosa*

Plan for Revision for all organisms/tables:

- Review literature and update current list of references for the Table being updated or created. Determine if any current references should be deleted
- Contact individuals who may have unpublished data
- Determine if method, QC ranges, and breakpoints are appropriate
- For each new organism, determine if existing CLSI methods can be used
- Determine if a limited amount of supplemental testing would be useful for the proposed changes or new additions (eg, growth studies, broth microdilution, disk diffusion)
- Update Supplemental Information section of table

**** Request to the Subcommittee for MIC Data on the below organisms:**

- *Aerococcus* spp.
- *Gemella* spp.
- *Lactococcus* spp.
- *Micrococcus* spp.
- *Rothia mucilaginosa*
- Genera related to *Bacillus* spp. (*Brevibacillus, Lysinibacillus, Paenibacillus*)

VII. REPORT OF THE FLUOROQUINOLONE AD HOC WORKING GROUP (Electronic Folder 7)

Chairholder: Dr. Karen Bush
Co-Chairholdr: Dr. Helio Sader

Working Group Members: Bob Flamm (Recording Secretary), Jeff Alder, Sujata Bhavnani, George Eliopoulos, Marcelo Galas, Romney Humphries, Elizabeth Palavecino, Mair Powell, Barth Reller, Robert Skov, Lauri Thrupp, Mel Weinstein, Barbara Zimmer

1. Summary of Surrogate Fluoroquinolone Disk Diffusion Testing

- EUCAST currently recommends pefloxacin as a surrogate disk diffusion assay for *Salmonella* spp. to predict fluoroquinolone (FQ) resistance based on 3 lab testing (EUCAST, Denmark, CDC)
- WG discussed the use of pefloxacin, as a surrogate disk test, based primarily on EUCAST data
- UCLA data suggests other FQs may be used
- Technical questions raised:

  - False resistance seen with pefloxacin in 8 isolates – may be due to quality of frozen plates at European testing sites
  - Clarity of zones with ciprofloxacin (EUCAST) and pefloxacin (UCLA)

Peflox 5 vs Cipro MIC

For all 8 isolates, 1 lab had an MIC of 0.125 but 2 labs had 0.064

All QC readings for ciprofloxacin were at the lower limit of the QC range and thus MICs of the clinical isolates 1 dilution too low.

Zone diameter	MIC (mg/L)						
	<0.016	0.032	0,064	0.125	0.25	0.5	1
6						2	
10					1	1	
11						1	
12					1	13	
13					3	28	
14				1	8	32	1
15			1	10	15	30	
16			1	10	18	20	5
17				24	33	7	
18			2	35	18	4	
19			9	42	6		
20			10	39	8		
21			13	20	5		
22			7	5	4		
23			4				
24	1		1				
25	2						
26	28						
27	51						
28	73						
29	63						
30	21						
31	11						
32	5						
33	2						
34	1						

Pefloxacin 5 µg Zones[1]

[1] BBL MHA II (single lot); Oxoid disks (single lot); 18 h incubation 20/47 ciprofloxacin non-susceptible isolates appeared similar. Deak et al. CLSI Jan. 2014

Future Plans: Surrogate FQ Disk Diffusion Testing – June 2014

- Additional clarification will be provided for:
  - Retesting of the 8 isolates with false resistance in EUCAST studies (pefloxacin disks)
  - EUCAST, Denmark and CDC labs
- More details/photographs will be provided regarding colonies within zone of clearing
- Recommendation for surrogate testing to be made in June 2014:
  - Which FQ?
  - Surrogate or screening test?
    - Not all fluoroquinolones are affected by all resistance mechanisms (levofloxacin with AAC(6')-Ib-cr)

2. Consideration of Fluoroquinolone Listings in Tables 2F and 2G

Text and Tables WG requested that the FQ WG review Tables 2F (*Neisseria gonorrhoeae*) and 2G (*Streptococcus pneumoniae*) FQ antimicrobial agents listed to see if the tables can be cleaned up and unused agents removed.

- Table 2F -- *Neisseria gonorrhoeae*

Agent	FDA Status (Drugs@FDA)
Ciprofloxacin	Active
Enoxacin	Discontinued
Gatifloxacin	Ophthalmic use only
Grepafloxacin	Discontinued
Lomefloxacin	Discontinued
Ofloxacin	Ophthalmic use only

Trovafloxacin	Discontinued
Fleroxacin	Not Available

- FQ WG Vote to retain only ciprofloxacin: 13 Yes, 0 No;
- **Subcommittee Vote: Approved 11-0; 1 Absent**

- Table 2G -- *Streptococcus pneumoniae*

Agent	FDA Status (Drugs@FDA)
Gemifloxacin	Active
Grepafloxacin	Discontinued
Levofloxacin	Active
Moxifloxacin	Active
Ofloxacin	Ophthalmic use only
Sparfloxacin	Discontinued
Trovafloxacin	Discontinued

- FQ WG Vote to retain only gemifloxacin, levofloxacin and moxifloxacin: 13 Yes, 0 No; **Subcommittee Vote: Approved 11-0; 1 Absent (a later note was made to include keeping gatifloxacin as well [currently listed in Table 2G]).**

3. Re-evaluate FQ Breakpoints for *Enterobacteriaceae*?

WG Motion 1: Conditions exist such that the subommittee should re-evaluate FQ breakpoints for enteric bacteria.

- Discussion: Three of four M23 conditions may have been met to suggest that FQ breakpoints need to be recalibrated
  - Updated PK/PD analyses, new resistance mechanisms, population analyses of recent clinical isolates.
  - Sufficient clinical data are sparse and probably not attainable.
  - Data should be evaluated at a forthcoming CLSI meeting

FQ WG Vote: 13 Yes, 0 No

Motion 2: Moxifloxacin should be included in Table 2A when all FQ breakpoints are being re-evaluated.

- Discussion: Moxifloxacin has FDA breakpoints but no CLSI breakpoints for *Enterobacteriaceae*
- If other FQ breakpoints are lowered, moxifloxacin is not on a level playing field and would have an advantage
- Unease about introducing this into Table 2A with no additional evaluation

FQ WG Vote: 3 Yes, 9 No, 1 Abstain

Motion 3: When the BP WG determines whether conditions exist to re-evaluate FQ breakpoints for *Enterobacteriaceae*, moxifloxacin should be included in that analysis.

- Discussion: Sponsor will not be able to provide a full M23 presentation

FQ WG Vote: 10 Yes, 0 No, 3 Abstain

The FQ WG requested that the Breakpoint WG consider motions 1 and 3 as they determine future work to be done.

VIII. GC BREAKPOINT AD HOC WORKING GROUP UPDATE (Electronic Folder 8)

Co-Chairholders: Dr. John Papp and Dr. Vanessa Allen; Guidance provided by Dr. Mary Jane Ferraro
Members: Robert Kirkcaldy, Sarah Kidd,Kathryn Lupoli

Dr. Allen provided background as well as an overview on the work being done to work towards defining breakpoints for cefixime, ceftriaxone and azithromycin for gonorrhea. Current treatment recommendations for uncomplicated urogenital, rectal or pharyngeal gonorrhea in the U.S. is as follows:

Recommended regimen:

- Ceftriaxone 250 mg in a single intramuscular dose

PLUS
- Azithromycin 1 g orally in a single dose

or doxycycline 100 mg orally twice daily for 7 days

Alternative, if ceftriaxone is not possible (for pharyngeal infections only ceftriaxone + azithromycin is recommended (ie there is no alternative therapy recommendations - A test of cure is recommended in the case of alternative treatment regimens):

- Cefixime 400 mg in a single oral dose

PLUS
- Azithromycin 1 g orally in a single dose

or doxycycline 100 mg orally twice daily for 7 days

If the patient has severe cephalosporin allergy:
- Azithromycin 2 g in a single oral dose

Evidence to re-evaluate breakpoints include:
- Gradual decrease in susceptibility of the gonococcus to cephalosporins; more pronounced for cefixime than for ceftriaxone.
- Cefixime treatment failures and decreasing susceptibilities have now been reported in Asia, Europe and Canada.

- For azithromycin MICs among circulating strains of *Neisseria gonorrhoeae* have seen sporadic high level azithromycin resistant isolates (> 256 μg/mL) - US, Argentina, Scotland, Italy, Canada, England
- Have good information for the molecular basis of elevated cephalosporin and macrolide MICs in *Neisseria gonorrhoeae* as shown below:

Ceftriaxone Cefixime	• Mosaic PBP2 (elevated MICs with specific mutations eg. G545S, I312M, V316T, G542, P551, A501P) • Amino acid substitutions in the porin gene, *porB* (eg. G120K and A121N) • Deletions or insertions in the *mtrR* gene that regulates for the *mtr*CDE efflux pump	• => 0.12 μg/mL
Azithromycin	• Mutations in the 23S rRNA (eg C2599T) • Deletions or insertions in the *mtrR* gene that regulates for the *mtr*CDE efflux pump	• => 2 μg/mL associated with mutations in 4/4 copies of 23S • 1 μg/mL has been associated with mutation in 1-2/4 copies of 23S

- Have limited data right now for clinical treatment failures of *N. gonorrhoeae* infections associated with elevated MICs to the cephalosporins and azithromycin outside of original therapeutic studies (with wild type strains). Test of cure recently introduced in the US for alternative treatments and now routinely recommended in the UK, so hopefully this will allow to obtain more data.

Conclusions:

- The recommended treatment for *N. gonorrhoeae* is limited to ceftriaxone, cefixime and azithromycin (and doxycycline)
  - Resistance breakpoints have not been defined for these drugs for *N. gonorrhoeae* by CLSI
  - Increased MICs to ceftriaxone, cefixime and azithromycin worldwide
  - Molecular mechanisms of elevated MICs are well defined
  - Some PK/PD data for the cephalosporins and *N. gonorrhoeae*
  - Clinical failures associated with increased MICs in case reports and historical cohort study
- Implication for both clinical applications and guideline development

Next Steps:

- Azithromycin QC range proposal for ATCC 49226 (in progress)
  - Routine data from 7 labs available (> 300 data points/ year)
  - Lot and manufacturer variation
  - Disk diffusion QC range to be performed
  - To be presented to the QC working group in June 2014
- Preparing dossier for breakpoint re-evaluation for *N. gonorrhoeae* for cefixime, ceftriaxone, and azithromycin

- Link with EUCAST
- Initial dossier for cefixime and ceftriaxone with currently available data to be brought forward to breakpoint working group in June 2014

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

Co-Chairholder – Dr. Steven Brown
Co-Chairholder – Ms. Sharon Cullen (absent)

Members Present: Bill Brasso, Janet Hindler, Erika Matuschek, Ross Mulder, Susan Munro, Bob Rennie

Members Absent: Patti Conville, Stephen Hawser, Michael Huband, Ron Jones, Frank Wegerhoff

1. CDC recommendations: Azithromycin QC for *N gonorrhoeae*. Presentation informational. Seeing increase resistance with resistance and decreased susceptibility. Surveillance (GISP) began in1995. Surveillance includes 5 reference labs and 25-30 CDC clinical labs. Males only urethral.

   a. QC data for azithromycin vs. *N. gonorrhoeae* ATCC® 49226 was presented. Most observations were between 0.25-1 µg/mL. The working group provided recommendations for bringing the data into compliance with M23.

2. Environmental breakpoint (wild type cut-off). Presentation informational:

   a. Standard practice, ceftriaxone and Azithromycin combination or Doxycycline. No CLSI breakpoints for Azithromycin and *N. gonorrhoeae* and only susceptible only for Cefotaxime

   b. A proposal was made to established epidemiological cutoff for *N. gonorrhoeae* to azithromycin agar dilution as ≤1.

   c. The QC Working group agreed that a working group be created to address epidemiological cutoffs for multiple drugs. Need to address epidemiological cutoff in M23.

The Subcommittee approved all QC ranges and proposed text changes as shown below in this report (Approved 10-0; 1 abstain, 1 absent):

3. Ceftazidime and Ceftaroline QC ranges for *K. pneumoniae* ATCC® 700603, presented by Maria Traczewski.

   a. Ceftazadime 16-64 (100% In Range). WG vote 7/0/0/6 (in favor/opposed/abstain/absent). See table below:

CLSI January 2014 San Antonion, TX						
Report of the QC Working Group						
Name	Ceftazidime	Previous ID		Abbrev	CAZ	WG Votes (For/Opposed/Abstained/Not present) Total 7/0/0/6
Solvent	sodium carbonate	Diluent	water			
Route of Administration	IM & IV	Class	CEPHEM	Subclass	CEPHALOSPORIN III	
QC Strain (ATCC)	Acceptable	# mm or dil	% In range	Median	Shoulder	Variability/Comments
K. pneumoniae ATCC 700603		16-64 µg/ml	100.0%	32	none	7/0/0/6

b. Ceftaroline 2-8. (97.5% In range). WG vote 7/0/0/6 (in favor/opposed/abstain/absent). See Table below:

Name	Ceftaroline	Previous ID		Abbrev	CPT	WGVotes (For/Opposed/Abstained/Not present) Total 7/0/0/6
Solvent	DMSO to 30% of total volume	Diluent	Saline			
Route of Administration	IV	Class	CEPHEM	Subclass	CEPHALOSPORIN with anti-MRSA activity	
QC Strain (ATCC)	Acceptable	# mm or dil	% In range	Median	Shoulder	Variability/Comments
K. pneumoniae ATCC 700603		2-8 µg/ml	97.5%	4	none	7/0/0/6. 6 rresults out of range on high end.

4. GSK 2140944 Disk Ranges, presented by Bob Flamm. New class of drug, nucleic acid inhibitor

   a. *S. aureus* ATCC® 25923 23-29 mm if exclude Lab G. (96.4% in range). WG vote 6/1/0/6.

   b. *E. coli* ATCC® 25922 18-26 mm. (98.7% In range) WG vote 7/0/0/6

   c. *H. influenzae* ATCC® 49247. **No range recommended** due to media affect and extreme reader variability. WG vote 7/0/0/6

   d. *S. pneumoniae* ATCC® 49619 22-28 mm excluding lab C. (99.4% In range) WG vote 7/0/0/6.

See Table below:

Route of Administration		Class	bacterial type II topoisomerase inhibitor	Subclass		
QC Strain (ATCC)	Acceptable	# mm or dil	% In range	MODE	Shoulder	Variability/Comments
S. aureus ATCC 25923		23-29 mm	96.4%	26		6/1/0/6. The person voting against this ranges wanted to exclude 23mm.
E. coli ATCC 25922		18-26 mm	98.7%	22		7/0/0/6
H. influenzae ATCC 49247		No range recommended		20		No range recommended due to media affect and extreme reader variability. 7/0/0/6
S. pneumoniae ATCC 49619		22-28 mm	99.4%	25		7/0/0/6 Excluding lab C as a statistical outlier.

5. Replace *E. coli* ATCC® 35218 with *K. pneumoniae* ATCC® 700603 for routine testing of non-Fastidious organisms.

   a. A motion was made to <u>postpone a decision</u> till June and see a mockup of the table. WG Vote: 6 in favor, 1 opposed 0 abstained, 6 absent.

   b. The likely mockup of the table is shown below (to be listed in alphabetical order. See. Page 156 of M100-S24 for current table as seen in **BLACK**):

Quality Control Ranges for *Klebsiella pneumoniae* ATCC® 700603* as supplemental QC (to be arranged in alphabetical order).

Antimicrobial Agent	*Klebsiella pneumoniae* ATCC 700603
Aztreonam	**8–64**
Aztreonam-avibactam	**0.06/4–0.5/4**
Biapenem	**0.03–0.12**
Ceftaroline-avibactam	**0.25/4–1/4**
Ceftazidime-avibactam*	**0.25/4–2/4**
Ceftolozane-tazobactam	**0.5/4–2/4**
Amoxicillin-clavulanic acid	**4/2-16/8**
Ampicillin or Amoxicillin	**>128**
Ampicillin-sulbactam	**8/4-32/16**
Ceftaroline	**2-8**
Ceftaroline-avibactam	**0.25/4-1/4**
Ceftazidime	**16-64**
Ceftazidime-avibactam	**0.25/4-2/4**

Piperacillin	**--****
Piperacillin-tazobactam	**8/4-32/4**
Ticarcillin	**>256**
Ticarcillin-clavulanic acid	**32/2-128/2**

**K. pneumoniae* ATCC® 700603 should be tested against ceftazidime-avibactam and ceftazidime alone or ceftaroline/avibactam and ceftaroline alone to confirm the activity of avibactam in the combination and to ensure that the plasmid encoding the ß-lactamase has not been lost in this strain. Any of the above β-lactams can be used to test the strain for loss of plasmid. It is not necessary to test each one.

**No range recommended due to off-scale results on the low end.

6. User QC questions and proposed revisions.

   a. Item #1. Modify Footnote M100, M02, M07 to clarify QC testing of *E. coli* ATCC® 35218. 7/0/0/6.

• **Recommended modification Table 4A Disk footnote c and Table 5A MIC footnote c,** "It is essential that *E. coli* ATCC® 35218 maintains its ability to produce beta-lactamase in order to adequately QC beta-lactam/beta-lactamase inhibitor agents. If stored at temperatures above -60 Co or if repeatedly subcultured, *E. coli* ATCC® 35218 may lose its plasmid containing the genes that code for beta-lactamase production. To ensure *E. coli* ATCC® 35218 maintains its beta-lactamase production integrity, subculture from a frozen or lyophilized stock culture at least monthly and subsequently test by disk diffusion or MIC with either ampicillin, or piperacillin, or ticarcillin. In range QC results for these agents confirms that the subculture of *E. coli* ATCC® 35218 is reliable for QC of the beta-lactam/beta-lactamase inhibitor agents (refer to M02-A12 Section 15 and M07-A10 Section 16.___)."

   b. Item #2. Clarify Table 2E *Haemophilus* Routine QC box instructions. 7/0/0/6.

Routine QC Recommendations (See Tables 4A, 4B, 5A, and 5B for acceptable QC ranges.) *Haemophilus influenzae* ATCC® 49247 *Haemophilus influenzae* ATCC® 49766 Use either *Haemophilus influenzae* ATCC 49247 or *Haemophilus influenzae* ATCC 49766 or both of these strains, based on the antimicrobial agents to be tested. Neither strain has QC ranges for all agents that might be tested against *H. influenzae* or *H. parainfluenzae*. *Escherichia coli* ATCC® 35218 (when testing amoxicillin-clavulanic acid)

c. Item #3. Clarify best QC method for *S. pneumoniae* ATCC® 49619 vs. oxacillin disk. WG 7/0/0/6.

> **Routine QC Recommendations** (See Tables 4B and 5B for acceptable QC ranges.)
>
> *Streptococcus pneumoniae* ATCC® 49619
>
> Disk diffusion: deterioration of oxacillin disk content is best assessed with Staphylococcus aureus ATCC 25923, with an acceptable range of 18-24 mm on unsupplemented Mueller-Hinton agar.

7. Quality Control Tier 3 Monitoring

   a. *E. coli* ATCC 25922 vs. Amp disk. Change range from 16-22mm to 15-22mm. WG vote 7/0/0/6.

   b. Continued Tier 3 monitoring of:

      i. Meropenem disk diffusion vs. *P. aeruginosa* ATCC®27853

      ii. *E. faecalis* ATCC® 29212 vs. Teicoplanin

X. M23 WORKING GROUP UPDATE

Co – Chairholders – Dr. Mair Powell and Mr. Kerry Snow
Working Group Members: Halsey Boyd, Patricia Bradford, Sharon K. Cullen, Denise Holliday, Seong Jang, Margaret Ordóñez Smith de Danies, Ryan Owen, John Rex, Daniel Rubin, Hala Shamsuddin, Sharon Shinn, John Turnidge, Thamban Valappil, Mel Weinstein, Matt Wikler

Dr. Powell gave an overview on the work to date for the revision of the M23 document. The WG has held 3 conference calls since their initial face-to-face meeting last June and have put together a revised draft outline. The contents have been reorganized to put them in a more logical order as follows:

- Usual Scope and Terminology which will be updated
- QC - this will be arranged in 3 subsections with each outlining what to submit:
  - Procedures for adding or amending QC strains or ranges
  - QC strains
  - QC ranges
- Interpretive criteria – this will be split into 3 major areas:
  - Procedures for adding or amending interpretive criteria including how and when to submit a request as well as process to handle request.

- What to submit to support MIC interpretive criteria – the M23 WG is working closely with the PK/PD WG on this piece whis is broken out into 4 sections:
  - Section on microbiological data outlining what CLSI and FDA would like to see
  - PK/PD section
  - Section on clinical data
  - Section on weighting of data
- What to submit to support disk diffusion interpretive criteria

The WG will be continuing to work via teleconference to try and have a close to final draft for discussion at the June meeting.

XI. REQUEST TO ESTABLISH A VANCOMYCIN RESISTANT BREAKPOINT FOR GROUP B STREPTOCOCCI (Electronic Folder 10)

Ms. Janet Hindler and Dr. Jim Jorgensen

Part of the meeting agenda materials included a letter from Dr. Bernie Beall from CDC describing two strains of Group B Strep and one strain of *Sreptococcus anginosus* with elevated vancomycin MICs. The two cases of Group B Strep strains will be part of a manuscript that will be published in the New England Journal of Medicine. Dr. Jorgensen presented these patient cases as follows:

Patient 1:

- 82 yo female; past history of DM
- Presented to NYC ER with fever, right ankle pain with swelling and drainage 8 weeks after open fracture repair
- CT: intra-articular gas
- Started on vancomycin empirically
- Blood and wound cultures: GBS with vancomycin MIC of 4 µg/mL (NS) *and* MRSA
- Excision and drainage plus 6 wks daptomycin followed by linezolid

Patient 2:

- 48 yo male with end stage renal disease on hemodialysis; severe penicillin allergy
- Presented to New Mexico ER with fever and right chest wall erythema
- Recently completed 8 wks of vancomycin for GBS bacteremia from left hip sacroilitis
- Started on 500 mg vancomycin after dialysis
- Admission blood culture positive for GBS with vancomycin MIC of 4 µg/mL (NS)
- Infection resolved without further treatment

Patient 3:

- Young female in MN post MVA
- Extended hospitalization
- Prior history of MRSA and vancomycin therapy
- Received vancomycin in May, 2012
- June 3, 2012 – fever and vomiting
- Urine culture: non-hemolytic *S. anginosus* with vancomycin MIC of 4 µg/ml (NS)

CDC characterized these three strains and found they all contain the *vanG* elements seen initially in enterococci. CDC requested that CLSI develop vancomycin resistance breakpoint of $\geq$ 2 µg/mL for β-hemolytic and viridans group streptococci.

Options for the subcommittee to consider:

1. Vancomycin S $\leq$ 1 and R $\geq$ 2 µg/mL (CDC Request)
2. Vancomycin S, I, R of 1, 2, 4 µg/mL
3. Leave as is, (NS) since vancomycin resistance in streptococci is "rare" so far
   - NS = "Absence or rare occurrence of resistant strains"

A motion was made to accept option 3 to leave the breakpoint as is and this was approved by the subcommittee **Approved 11-0; 1 absent.**

XII. REPORT OF THE TEXT AND TABLES WORKING GROUP (Electronic Folder 11)

Co - Chairholder – Ms. Jana Swenson

Co - Chairholder – Ms. Maria Traczewski

Members Present: Janet Hindler, Dyan Luper, Linda Mann, Susan Munro, Flavia Rossi, Dale Schwab, Tom Thomson, and Mary York

Members Absent: Jeffrey Schapiro

Items for Information:

The working group reviewed M02 between the June and January meeting and all reviews were collated into one document. Four items from the review were discussed at the working group meeting to present to the subcommittee for a vote.

The plan forward will be for Ms. Dooley to incorporate all the appropriate changes made in M02 into M07. Both documents will then be circulated to the WG members for final review. Comments from this review will be considered and discussed in a teleconference in early March. The WG will then make any changes required and send both documents to Ms. Dooley for distribution to the subcommittee members and advisors for review and comment sometime in April.

M100 will be reviewed by the WG and comments and changes will be discussed at a second teleconference in April. M100 changes to be recommended will be decided at this time and a copy will be circulated to the subcommittee for comment in late April.

Items for Vote by Subcommittee:

1. M02 Section 5, 2nd paragraph

5 Indications for Performing Susceptibility Tests (2nd paragraph):

Isolated colonies of each type of organism that may be pathogenic should be selected from primary agar plates and tested individually for susceptibility. Identification procedures are often performed at the same time. Mixtures of different types of microorganisms should not be tested on the same susceptibility test plate. The practice of conducting susceptibility tests directly with clinical material (eg, normally sterile body fluids and urine) should be avoided, except in clinical emergencies when the direct Gram stain suggests a single pathogen. When testing has been carried out directly with the clinical material, results should be reported as preliminary, and the susceptibility test must be repeated using the standardized methodology.

WG discussed this section and decided that direct specimen susceptibility testing should be discouraged.

The following change was voted on by WG 12-0 in favor:

Isolated colonies of each type of organism that may be pathogenic should be selected from primary agar plates and tested individually for susceptibility. Identification procedures are often performed at the same time. Mixtures of different types of microorganisms should not be tested on the same susceptibility test plate. The practice of -Conducting susceptibility tests directly with clinical material (eg, normally sterile body fluids and urine) is not standardized and should not be done.

The subcommittee voted to accept the following: Approved 10-1; 1 absent

Isolated colonies of each type of organism that may be pathogenic should be selected from primary agar plates and tested individually for susceptibility. Identification procedures are often performed at the same time. Mixtures of different types of microorganisms should not be tested on the same susceptibility test plate. Conducting susceptibility tests directly with clinical material (eg, normally sterile body fluids and urine) is not standardized and should not be done.

2.) 11.1.2 Methicillin/Oxacillin Resistance

11.1.2.1 **Background**

Historically, resistance to the antistaphylococcal, penicillinase-stable penicillins (eg, methicillin, nafcillin, oxacillin, cloxacillin, flucloxacillin and dicloxacillin) has been referred to as "methicillin resistance," and the acronyms "MRSA" (for methicillin-resistant *S. aureus*) or "MRS" (for methicillin-resistant staphylococci) are still commonly used, even though methicillin is no longer the agent of choice for testing or treatment. In this document, resistance to these agents may be referred to using several terms (eg, "MRS," "methicillin resistance," or "oxacillin resistance"). Most resistance to oxacillin in staphylococci is mediated by the *mec*A gene, which

directs the production of a supplemental penicillin-binding protein, PBP 2a, and, during bacterial cell replication, is expressed either homogeneously or heterogeneously. Homogeneous expression of resistance is easily detected with standard testing methods since nearly all bacterial cell progeny express the resistance phenotype. Heterogeneous expression may be more difficult to detect because only a fraction of the progeny population (eg, 1 in 100 000 cells) expresses resistance. In the past, the presence of resistance to other antimicrobial agents outside the β-lactam class suggested an isolate was methicillin resistant. However, some contemporary MRSA strains, such as those found in community-associated infections, are not multidrug resistant, and an increasing number of MSSA strains are more resistant to a broad range of antimicrobial classes.

WG discussed the last sentence as possibly being misleading at this time and voted to remove the last sentence in red. **WG Vote 12-0 in favor**

The subcommittee agreed and approved the change. Vote: Approved 11-0; 1 absent

3.) 11.1.2.3 Methods for Detection of Oxacillin Resistance (2nd bullet)

For oxacillin-based tests, incubate tests to detect MRS for a full 24 hours at 35 ± 2°C (testing at temperatures above 35°C may not detect MRS, especially when using oxacillin) before reporting as susceptible. Oxacillin is the preferred antistaphylococcal penicillin to use because it is more resistant to degradation in storage. The addition of NaCl (2% w/v; 0.34 mol/L) is required for both agar and broth dilution testing of oxacillin to improve the detection of heteroresistant MRSA.

The WG discussion revolved around the section in red which seemed to be contradictory to the instruction before it in the same sentence. The WG voted to remove the parenthetical information because it is contradictory. WG voted: 12-0 in favor

There was disagreement among the subcommittee members, advisors and reviewers on removing this section. After much discussion it was decided that the working group would go back and find a way to remove this section from the sentence but still give the instruction about keeping the incubation temperature at 30 -35° C somewhere else in this section. **No Change at this time.**

4.) Suggestion to Remove the following table from 11.1.3.1 and 12.1.3.1 in M2 and M7

Ability of Various Methods to Detect Levels of Vancomycin Susceptibility in *S. aureus*

Vancomycin MIC (µg/mL)	MIC Method	Disk Diffusion Method*	Vancomycin Agar Screen
≤ 2 (S)	Yes	No	Yes
4 (I)	Yes	No	Variable
8 (I)	Yes	No	Yes
16 (R)	Yes	No	Yes
≥ 32 (R)	Yes	Yes	Yes

* Strains of *S. aureus* for which the vancomycin zone diameter is ≥ 7 mm may have MICs from ≤ 2 to 16 µg/mL. If disk diffusion testing is performed, the identification of isolates showing no zone of inhibition should be confirmed. Isolates of *S. aureus* producing vancomycin zones of ≥ 7 mm should not be reported as susceptible without performing a vancomycin MIC test.

WG voted 11-1 to remove the entire table since the disk diffusion test had already been removed from M100 and the performance of the agar screen test is discussed separately in both M2, M7 and M100.

Subcommittee agreed with WG decision: Approved 11-0; 1 absent

XIII. PK/PD AD HOC WORKING GROUP UPDATE

Co – Chairholders – Dr. Linda Miller and Dr. Paul Ambros
Working Group Members: Eileen Kim (Recording Secretary), Bill Craig (recently retired from WG), Seong Jang, Jim Lewis, Ryan Owen, Elizabeth Palavecchino, John Turnidge

WG Goal:

To provide guidance on key components of PK/PD studies, data, analysis and presentations in support of breakpoint requests to CLSI to provide improved consistency and increased quality.

- First Task: Update PK/PD Section of M23
- Second Task: Recommend to AST SC if a separate PK/PD Document is needed

Keeping with the timeline that the M23 WG has set, the first draft of the PK/PD section is complete and was reviewed on Sunday during a meeting of the WG.

- Next Draft for M23 WG review February/March 2014
  - Will also obtain some wider review outside of the PK/PD and M23 WG

- Will present proposed draft of the PK/PD section to AST SC in June

XIV. SALM ONELLA/AZITHROMYCIN AD HOC WORKING GROUP UPDATE

Co – Chairholders – Mr. Marcelo Galas and Dr. John Turnidge
Working Group Members: Paul Ambrose, John Crump, Maria Karlsson

Mr. Galas gave a brief overview on the effort of this WG to set azithromycin breakpoints for *Salmonella*. On the conference calls held by the WG to date, they have reviewed available data and determined that more clinical data was necessary; have microbiological data and some PK/PD data but don't have correlation between PK/PD and outcomes in patients. There is an increasing problem with resistance of *S. typhi* to fluroquinolones and because of this, countries are using azithromycin for which CLSI has no recommendaitons.

Data that the WG is reviewing includes:

- Correlation data from CDC – MIC and disk diffusion in 419 strains as well as interlaboratory comparison data of the test reproducibility
- Results recently available from work conducted by Chris Parry – 1,750 strains of *S. tyhi* and *S. paratyphi*: MIC and disk diffusion correlation data as well as characterization of resistance mechanisms. Also outcome data in 200 cases.
- Work currently being done in Latin America using 350 strains to see MIC (broth microdilution and agar dilution) and disk diffusion correlation as well as characterization of resistance mechanisms.

The WG plans to present all data in June and propose a recommendation to the subcommittee.

XV. AGENDA SUBMISSIONS FOR 29 JUNE-1 JULY 2014 MEETING IN SAN DIEGO

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 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 29 June- 1 July 2014 meeting please:

1) Submit agenda materials electronically as a PDF file **on or before Friday, 23 May 2014.**

   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), Franklin R. Cockerill, III, MD (cockerill.franklin@mayo.edu) please copy his Administrative Assistant JoAnn Brunette (Brunette.Joann@mayo.edu) and also to Tracy Dooley (tdooley@clsi.org) for review.

Note: The 29 June – 1 July 2014 meeting will be held in San Diego, California at the Westin San Diego Gaslamp Quarter. Additional meeting details will be provided in March when the announcement is circulated.

XIV. ADJOURNMENT – The meeting adjourned at 4:20 p.m. on Monday, 13 January 2014.

Respectfully submitted,

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