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Summary Minutes
Subcommittee on Veterinary Antimicrobial Susceptibility Testing
Hyatt Regency Mission Bay
San Diego, California
8-9 January 2009

A meeting of the Subcommittee on Veterinary Antimicrobial Susceptibility Testing was held on 8-9 January 2009, at the Hyatt Regency Mission Bay in San Diego, California. The following were in attendance:

Jeffrey L. Watts, PhD, RM(AAM)
Chairholder

Pfizer Animal Health

Mark G. Papich, DVM, MS
Vice Chairholder

North Carolina State University

Members Present

Donald J. Bade
Steven D. Brown, PhD
Virginia R. Fajt, DVM, PhD, DACVCP
Henry Heine, PhD
Rob P. Hunter, MS, PhD
Peter Silley, PhD
Robert D. Walker, PhD
Ching Ching Wu, DVM, PhD

Microbial Research, Inc.
The Clinical Microbiology Institute
Texas A & M University
USAMRIID
Elanco Animal Health
MB Consult Limited
Anti-Infectives Research Consultants, LLC
Purdue University School of Veterinary
Medicine
Micromyx, LLC

Gary E. Zurenko, MS

Advisors Present

Melanie R. Berson, DVM
Diane M. Citron, M(ASCP)
Ronald N. Jones, MD
Cindy Lindeman
Jennifer Lorbach
Marilyn N. Martinez, PhD
Patrick McDermott, PhD
Stefan Schwarz, DVM
Thomas R. Shryock, PhD
Clyde Thornsberry, PhD
John D. Turnidge, MD
S. Steve Yan, PhD

FDA Center for Veterinary Medicine
R.M. Alden Research Laboratory
JMI Laboratories
Pfizer Animal Health
Trek Diagnostic Systems
FDA Center for Veterinary Medicine
FDA Center for Veterinary Medicine
Friedrich-Loeffler Institute
Elanco Animal Health
Eurofins Medinet
Women's and Children's Hospital
FDA Center for Veterinary Medicine

Observers Present

Tara Bidgood, DVM, PhD, DACVCP
Chander Celly
Timothy S. Frana, DVM, MS, MPH, PhD
Thomas R. Fritsche, PhD, MD
Dave Griffin
Joshua Hayes, PhD
Daniel J. Keil, DVM, PhD, DACVM
Scott B. Killian, BS
Cynthia C. Knapp, MS
Maureen Mansfield
Paul Rhomberg, MT (ASCP)
Markus Rose, DVM, PhD
Dr. Shabbir Simjee
Bernd Stephan
Michael Sweeney
Maria M. Traczewski, BS, MT(ASCP)
Michael B. Vaughn, DVM, MS

Pfizer Animal Health
Schering Plough Corporation
Iowa State University
JMI Laboratories
Quotient Bioresearch Ltd.
FDA, Center for Veterinary Medicine
Bayer Healthcare – Animal Health
Trek Diagnostic Systems
Trek Diagnostic Systems
Trek Diagnostic Systems
JMI Laboratories
Intervet Innovation
Elanco Animal Health
Bayer HealthCare AG
Pfizer Animal Health
The Clinical Microbiology Institute
Bayer Animal Health

CLSI Staff Present

Tracy A. Dooley, BS, MLT (ASCP)
Helen Gallagher
Cathy Johnson, MA, MT (ASCP)
Claire Schultz
Ellen L. Williams

Opening Remarks

Dr. Papich began the meeting Thursday, 8 January at 8:30 a.m. He stated that the purpose of Thursday's session was to provide an opportunity for the working groups to address their agenda topics and obtain input from the subcommittee.

A sponsor presentation and working group reports would be presented to the full subcommittee during Friday's session.

Minutes of Prior Meeting

The subcommittee voted to approve the summary minutes from the 24-25 January 2008 meeting held in Tampa, Florida (**Approved 9-0; 1 absent**).

Update on CLSI Publications

Ms. Dooley provided a brief update of recent and upcoming CLSI publications as well as new projects under development within the Area Committee on Microbiology as follows:

Recently Published Documents

M50-A, *Quality Control for Commercial Microbial Identification Systems; Approved Guideline*. Published September 2008.

M23-A3, Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters – Approved Guideline. Published October 2008.

M35-A2, *Abbreviated Identification of Bacteria and Yeast; Approved Guideline*. Published November 2008.

M2-A10, *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard-Tenth Edition*. Published January 2009.

M7-A8, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Eighth Edition*. Published January 2009.

M100-S19, *Performance Standards for Antimicrobial Susceptibility Testing; Nineteenth Informational Supplement*. Published January 2009.

Upcoming Publications

M39-A3, *Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data; Approved Guideline*. This document is estimated for publication at the end of January 2009.

New Projects Under Development

X7-R, Surveillance for Methicillin-Resistant *Staphylococcus aureus*: Principles, Practices, and Challenges; A Report - Co-Chairholders: Fred C. Tenover, PhD, ABMM and Cassandra Salgado, MD, MS

This report will describe the epidemiologic, scientific, and public health aspects of MRSA as well as the impact of resulting policies on health institutions. Evidence-based information on the technological choices and issues for implementation will be presented to assist laboratories that are faced with the prospect of adopting MRSA screening programs for their institution/community.

M51-P, *Method for Antifungal Disk Diffusion Susceptibility Testing of Filamentous Fungi* - Chairholder: Ana Espinel-Ingroff, PhD

This document will describe an agar diffusion disk method that would make the susceptibility testing of filamentous fungi to amphotericin B, itraconazole, posaconazole, voriconazole and caspofungin more readily available to the clinical laboratory.

M52-P, *User Verification of Microbial Identification and Antimicrobial Susceptibility Testing Systems* - Co-Chairholders: Linda M. Mann, PhD, D(ABMM) and Dee Shortridge, PhD

This document will provide general guidelines for microbiology laboratories on verification of new methods to be introduced into their laboratories with a focus on automated methods for

bacterial susceptibility and identification, using commercial systems. It will not address serological assays, assays developed in-house or molecular methods.

M53-P, *Criteria for Laboratory Testing and Diagnosis of HIV-1 Infections* - Chairholder: Eric Rosenberg, MD

This document will provide general guidelines for microbiology laboratories on verification of new methods to be introduced into their laboratories with a focus on automated methods for bacterial susceptibility and identification, using commercial systems. It will not address serological assays, assays developed in-house or molecular methods.

New Project Under Consideration

Specimen Collection, Handling, Processing, Set-up and Interpretation of Fungal Cultures

The intent of this document will be the creation of a standard for procedures for the collection of fungal specimens, their handling, processing and interpretation of culture results. Because the relative importance of any given fungus isolated from patient specimens depends upon the pathogenic potential of the fungus and the clinical setting in which it is isolated, the issues as well as factors to consider regarding the isolate's clinical significance will also be discussed.

A call for nominations to solicit participants to develop this document will go out in the next few weeks in CLSI's electronic newsletter (eNews).

Marketing and Education

Ms. Ellen Williams, Senior Director of Marketing at CLSI outlined potential marketing possibilities for the Veterinary documents and asked for suggestions from the subcommittee on things such as target audience and ways to publicize the availability of the newly updated vet documents. Anyone having suggestions or ideas please contact Ms. Williams.

Ms. Cathy Johnson, Education Manager at CLSI outlined the education efforts that CLSI has done recently including a teleconference given by Dr. Wu on the use of the M31 document which will be repeated again this Spring. CLSI will also be creating easy to use "quick guides" that labs can easily refer to for QC testing. CLSI would like to try and develop other useful bench tools with the assistance of the committee and Ms. Johnson asked if anyone has any ideas to please let her know.

Also, if anyone will be giving a talk on the use of the CLSI Veterinary documents please contact her so that CLSI may assist in promoting the talk.

AST Liaison Report

Dr. Bob Walker provided an update on the activities of CLSI and the AST subcommittee as it relates to the VAST subcommittee as follows:

- CLSI has updated their IT with new hardware and software, a new look to their website and new on-line store, as well as a new Forums communication system for use in standards development.
- Dr. Walker discussed CLSI's strategic plan which includes 4 main goals:

- Anticipate, identify, and respond to the needs of our current and potential customers;
 - Develop and deliver top-notch products and services, maintain & enhance our outstanding reputation for quality;
 - Strengthen CLSI's global recognition by providing leadership in standards-development and implementation; and
 - Strengthen the governance, financial base, and structure, and address business risk to carry out CLSI's vision, mission and values.
- CLSI/FDA Update – Dr. Walker discussed the process differences for setting breakpoints between FDA and AST vs. FDA and VAST:
 - AST-FDA
 - Breakpoints set by FDA during drug approval process
 - CLSI can review and accept or not accept
 - VAST-FDA
 - Breakpoints set by VAST following drug approval (optional)
 - FDA-CVM can review and accept or not accept
 - Text and Table Changes in M2 and M7 – Some of the major changes in these documents includes:
 - Redefinition of “OR”
 - An “or” between agents designates those agents for which cross-resistance and cross-susceptibility are nearly complete
 - Results from one agent connected by an “or” could be used to predict results for the other agent
 - When no “or” connects agents within a box, testing of one agent cannot be used to predict results for another either owing to discrepancies or insufficient data.
 - A screening test for high-level mupirocin resistance to include new mupirocin breakpoints (both disk diffusion and MIC) to indicate high-level mupirocin resistance in isolates of *Staphylococcus aureus* was added in M100.
 - The AST subcommittee is looking at reassessing carbapenem breakpoints.

Working Group Updates

International Harmonization Working Group

Working Group Participants – Chairholder Tom Shryock; Members – Peter Silley, Bob Walker, Dik Mevius, Stefan Schwarz, Jeff Watts, Ruby Singh, Bernd Stephan.

Dr. Tom Shryock provided an overview of the working group’s mission/goals including:

- Expand current CLSI document content (primarily M31) to possibly include:

- additional testing methods for organisms not currently in M31 (eg, test methods for *Brachyspira*, *H. parasuis*, *A. pleuropneumoniae*, etc.);
 - other testing methods that may be considered acceptable to the VAST (eg, Etest [gradient method], ring testing).
 - quality control values for those methods; other methods of generating QC that are compatible with CLSI methods; and
 - breakpoints and interpretive criteria for non-US approved therapeutic products.
- Outreach to encourage sponsors and other organizations to participate in the process and try to expand the M31 tables to include non-US approved products with same indications, dose, route as for US.

The working group requests the Generic Working Group assistance in putting together a prioritized list of drug/organism combinations that could be considered for inclusion in M31, then determine the best way to move forward to obtain data through a sponsor and/or use the Generic working groups method for the review of data for older drugs.

- Breakpoints and interpretive criteria for non-US approved therapeutic products – the working group discussed the potential of developing a CLSI Report to include epidemiological cutoff values and clinical breakpoints. This could possibly be a foundation to move data from the report to the M31 document once more data is available. The scope of this proposal will need to be further defined and reviewed.

Editorial Working Group

Working Group Participants – Chairholder Gary Zurenko; Members – Jo Abraham, Steve Yan, Melanie Berson, Jeff Watts, Bob Walker, Mark Papich, Henry Heine, Stefan Schwarz, Maria Traczewski, Ching Ching Wu.

Mr. Gary Zurenko outlined the goals of the working group and what they have been working on for the next edition of M31 to include:

- Updating Glossary 1 and the listed resistance mechanisms.
- Updating Table 3 and confirming availability and culture strain numbers currently listed in the table.
- Creating a mock up of animal-specific tables, retaining the gray shaded human breakpoints in if no animal-specific breakpoints are available. If animal specific breakpoints are available, list those breakpoints for that particular species.

For the animal-specific tables, the subcommittee suggested making one table for swine, cattle, bovine mastitis, and poultry and a second table for dogs, cats, and horses.

- Add text from M07-A8 regarding detection of inducible clindamycin resistance into the M31 text.

- Clarify text in M31 (Section 6.8.1.3) for reporting oxacillin resistant results to say “Report oxacillin-resistant staphylococci as resistant to all other penicillins, carbapenems, cepheems, and β -lactam/ β -lactamase inhibitors, regardless of *in vitro* test results with those agents”.

It was also discussed to create an appendix table outlining screening for inducible clindamycin resistance.

- Incorporate any changes from the International Harmonization working group.

The working group will create mock-up tables as listed above for review by the subcommittee in June.

Education Working Group

Working Group Participants – Chairholder Virginia Fajt; Members – Mike Apley, Bob Badel, Jennifer Lorbach, Tom Shryock, Ching Ching Wu.

Dr. Virginia Fajt outlined potential goals of the Education working group as follows:

- Promote standardized testing –create a template letter for sending to editors to make them aware and promote the CLSI VAST standardized testing methods in journal articles and reviews.
- Try to expand pool of reviewers of journal articles by creating a list of names to draw from and educate these reviewers what to look for when reviewing.
- Generate slide decks for presentations. The working group requests that any previous presentation slides be sent to Dr. Fajt to assist in creating a library of slides that would be available on the CLSI website for speakers to use for presentations. Include slides with definitions (eg what is a fastidious organism)
- Look into possibly holding a teleconference on how to interpret results from diagnostic labs for veterinarians.
- Create a list of organisms needed for QC testing and provide a list of suppliers and contact information.
- Draft a letter as a Subcommittee to veterinary diagnostic laboratories on the use of CLSI standards.
- Hold train the trainer sessions on the use of M31.

The Education working group will update the subcommittee on their progress at the next meeting.

Generic Working Group

Working Group Participants – Co-Chairholders Mark Papich and Ching Ching Wu; Members – Shabbir Simjee, Cindy Lindeman, Bruce Craig, John Turnidge, Bob Walker, Stefan Schwarz, Marilyn Martinez, Tara Bidgood.

Dr. Mark Papich outlined the current objective of the working group which is to propose interpretive criteria for 1st generation cephalosporins (cefazolin, cephalexin, and cephalothin) against bacterial isolates from canine and equine animals. Data to be used to determine breakpoints include microbiological data obtained by Dr. Wu from AVMA survey (MIC data

only) and PK-PD data, indications, doses from U.S. Pharmacopeia, MIC surveillance data from Germany provided by Dr. Schwarz, and consensus published literature.

Based on the obtained data, MICs of ≤ 2 , 4, ≥ 8 were proposed (**Approved 7-2; 1 absent**).

Below is the proposed organism list that the working group will bring back in June with a final version of the table and comments to go in the table regarding dosing and how breakpoints were derived.

Cephalothin

Dogs (skin and soft tissue)

Staphylococcus aureus
Staphylococcus pseudintermedius
(*S. intermedius*)
Streptococci - β -hemolytic group
Escherichia coli

Cefazolin

Horses (respiratory, genital tract)

Streptococci - β -hemolytic group
Escherichia coli

Dogs (skin and soft tissue, respiratory, urinary/genital)

Coagulase-positive staphylococci
Pasteurella multocida
Streptococci - β -hemolytic group
Escherichia coli

Additional objectives of the working group include:

- Expand on some of the drugs that now have veterinary-specific breakpoints based on new data (eg, currently have veterinary-specific breakpoints for ampicillin for dogs and horses and would like to expand this to swine).
- Priority list of antimicrobial agents that the working group will try to obtain data to set veterinary-specific breakpoints in the future include:
 - Amoxicillin-clavulanic acid
 - Penicillin - problem with this drug is the dose range is wide and differs among animal species
 - Trimethoprim-sulfamethoxazole
 - Erythromycin
 - Chloramphenicol
 - Vancomycin

Veterinary Mycoplasma Working Group

Working Group Participants –Chairholder Ching Ching Wu; Members – Joann Kinyon, Cecile Bebear, Mary Brown, Don Bade, Lynn Duffy, Roger Ayling, Ken Waites

Dr. Ching Ching Wu outlined the need for a Co-chairholder who can attend the VAST meetings and assist in the tasks of this working group. Any suggestions or interested parties please contact Dr. Wu.

Once the working is able to initiate their task of trying to standardize mycoplasma susceptibility testing, they will develop a protocol and initiate testing to establish QC for bovine mycoplasma (*M. bovis*) as this mycoplasma grows well and there are currently two methods that have been used with fairly good reproducibility

Campylobacter Working Group

Working Group Participants – Chairholder Bob Walker; Members – Tom Fritsche, Pat McDermott

Dr. Walker provided an overview of the activities of the working group. Currently there are methodology and QC recommendations for agar dilution and broth microdilution testing, but due to the difficulty in determining accurate and reproducible zone sizes (all or nothing phenomenon with zones), disk diffusion testing has not yet been validated. A 7-lab study had been conducted but the study participants had a problem with media during testing.

The working group will update the subcommittee at the next meeting.

Aquaculture Working Group

Working Group Participants – Co-Chairholders John Hawke and Renate Reimschuessel; Members – Takashi Aoki, Guillaume Blanc, Jeremy Carson, Beverly Dixon, Mauro Giacomini, Geert Huys, Ron Miller, Peter Smith, Temdoug Somsiri, Bob Walker, Jeff Watts, Ching Ching Wu

Dr. Ron Miller, a member of the working group was not able to attend but provided an e-mail update stating they are currently working on data and an approach to setting interpretive criteria for aquaculture pathogens.

Breakpoint Presentation

Enrofloxacin for Swine Respiratory Disease

Dr. Robert Walker presented data in support of placement of Enrofloxacin in Table 1, Group A, Swine as well as proposed interpretive criteria when testing swine respiratory disease pathogens as follows:

Table 1:

Group A — Veterinary-Specific Interpretive Criteria Primary Test and Report	<u>Swine</u>
	Ceftiofur
	Enrofloxacin
	Florfenicol
	Tiamulin
	Tilmicosin
	Tulathromycin

Table 2:

Antimicrobial Agent	Disk Content	Zone Diameter (mm)			MIC Breakpoint (µg/mL)		
		S	I	R	S	I	R
Enrofloxacin Swine (Respiratory Disease) <i>Pasteurella multocida</i> <i>Actinobacillus pleuropneumoniae</i> <i>Streptococcus suis</i> *	5 µg	≥ 23	19-22	≤ 18	≤ 0.25	0.5	≥ 1
	-	-	-	-	≤ 0.5	1	≥ 2

The proposed Table 1 placement and interpretive criteria were approved with the addition of the below comment to be added for *S. suis* (**Approved 8-1; 1 absent**).

S. suis Comment:

*Disk diffusion interpretive criteria have not been established. It is recommended that *S. suis* isolates be tested by MIC.

The subcommittee suggested that the sponsor look at the source and geographic distribution of the isolates for *S. suis* and possibly repeat the study with a larger number of isolates. It was also suggested to look at disk mass for enrofloxacin (5 µg vs. 10 µg disks).

Next Meeting

The next meeting of the Subcommittee is tentatively scheduled as a day and a half meeting on June 26-27 in Boston, MA. Additional information will follow shortly with specific meeting details.

Adjournment - The meeting adjourned at approximately 4:00 p.m. on 9 January 2009.

Respectfully submitted,

Tracy A. Dooley, BS, MLT (ASCP)
Standards Administrator