CLINICAL AND LABORATORY STANDARDS INSTITUTE®

6th Edition

VET01S

Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals

This document includes updated tables for the Clinical and Laboratory Standards Institute veterinary antimicrobial susceptibility testing standard VET01.

A CLSI supplement for global application.

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Clinical and Laboratory Standards Institute
P: +1.610.688.0100
F: +1.610.688.0700
www.clsi.org
standard@clsi.org

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Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals

Brian V. Lubbers, DVM, PhD, DACVCP
Dubraska V. Diaz-Campos, DVM, PhD
Stefan Schwarz, DVM
Michael T. Sweeney, MS
Joshua Hayes, PhD
Andrea T. Feßler, DVM, PhD
Donald J. Bade, BS
Robert Bowden, BS
Claire R. Burbick, DVM, PhD, DACVM
Keith DeDonder, DVM, PhD, DACVCP
Virginia R. Fajt, DVM, PhD, DACVCP
Merran Govendir, PhD, BVSc, FHERDSA, MANZCVSc
Lacie Gunnett, BS
Nicole M. Holliday, BA
Sara D. Lawhon, DVM, PhD, DACVM
Xian-Zhi Li, PhD
John Dustin Loy, DVM, PhD, DACVM
Kelli Maddock, MS, MLS(ASCP)M
Ron A. Miller, MS, PhD
Ian Morrissey, BSc, MBA, PhD, FRSM
K. Marcia Murphy, DVM, DACVD
Mark G. Papich, DVM, MS
Shabbir Simjee, MSc, PhD
S. Steve Yan, PhD
Jeffrey L. Watts, PhD, RM(NRCM), M(ASCP)

Abstract

The data in the tables are valid only if the methodologies in CLSI document VET01[1] are followed. This standard contains information about disk and dilution susceptibility test procedures for aerobic and facultatively anaerobic bacteria. Clinicians need information from the microbiology laboratory for treating and/or confirming treatment decisions for their patients with bacterial infections and depend heavily on this information for treating their seriously ill patients. The clinical importance of antimicrobial susceptibility test results demands that these tests be performed under optimal conditions and that laboratories have the capability to interpret results based on the most current breakpoints and interpretive categories for antimicrobial agents used in veterinary medicine.

The tables presented in VET01S represent the most current information for drug selection, interpretation, and quality control using the procedures standardized in VET01.[1] Users should replace previously published tables with these new tables. Changes in the tables since the previous edition appear in boldface type.

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Committee Membership

Subcommittee on Veterinary Antimicrobial Susceptibility Testing

Brian V. Lubbers, DVM, PhD, DACVCP
Chairholder
Kansas State University
USA

Dubraska V. Diaz-Campos, DVM, PhD
Vice-Chairholder
College of Veterinary Medicine,
Veterinary Medical Center,
The Ohio State University
USA

Stefan Schwarz, DVM
Committee Secretary
Freie Universität Berlin
Germany

Claire R. Burbick, DVM, PhD, DACVM
Washington State University
USA

Merran Govendir, PhD, BVSc, FHERDSA, MANZCVSc
The University of Sydney
Australia

Nicole M. Holliday, BA
Thermo Fisher Scientific
USA

Sara D. Lawhon, DVM, PhD, DACVM
Texas A & M University
USA

Xian-Zhi Li, PhD
Health Canada Veterinary Drugs Directorate
Canada

Ron A. Miller, MS, PhD
FDA Center for Veterinary Medicine
USA

Ian Morrissey, BSc, MBA, PhD, FRSM
Antimicrobial Focus Ltd.
United Kingdom

K. Marcia Murphy, DVM, DACVD
North Carolina State University, College of Veterinary Medicine
USA

Shabbir Simjee, MSc, PhD
Elanco Animal Health
United Kingdom

Michael T. Sweeney, MS
Zoetis
USA

Working Group on Editorial/VAST Breakpoint Tables

Michael T. Sweeney, MS
Chairholder
Zoetis
USA

Robert Bowden, BS
Committee Secretary
Beth Israel Deaconess Medical Center
USA

Claire R. Burbick, DVM, PhD, DACVM
Washington State University
USA

Dubraska V. Diaz-Campos, DVM, PhD
College of Veterinary Medicine,
Veterinary Medical Center,
The Ohio State University
USA

Virginia R. Fajt, DVM, PhD, DACVCP
Texas A & M University
USA

Merran Govendir, PhD, BVSc, FHERDSA, MANZCVSc
The University of Sydney
Australia

Sara D. Lawhon, DVM, PhD, DACVM
Texas A & M University
USA

Xian-Zhi Li, PhD
Health Canada Veterinary Drugs Directorate
Canada

Kelli Maddock, MS, MLS(ASCP)M
NDSU Veterinary Diagnostic Laboratory
USA

Ron A. Miller, MS, PhD
FDA Center for Veterinary Medicine
USA

Mark G. Papich, DVM, MS
College of Veterinary Medicine,
North Carolina State University
USA

Stefan Schwarz, DVM
Freie Universität Berlin
Germany

S. Steve Yan, PhD
FDA Center for Veterinary Medicine
USA

Working Group on Bovine Mastitis Interpretive Criteria

Joshua Hayes, PhD
Chairholder
FDA Center for Veterinary Medicine
USA

Andrea T. Feßler, DVM, PhD
Vice-Chairholder
Institute of Microbiology and Epizootics, Freie Universität Berlin
Germany

Donald J. Bade, BS
Committee Secretary
Microbial Research, Inc.
USA

Keith DeDonder, DVM, PhD, DACVCP
Latham BioPharm Group
USA

John Dustin Loy, DVM, PhD, DACVM
University of Nebraska-Lincoln
USA

Brian V. Lubbers, DVM, PhD, DACVCP
Kansas State University
USA

Stefan Schwarz, DVM
Freie Universität Berlin
Germany

Staff

Clinical and Laboratory Standards Institute
USA

Lori T. Selden, MS, MT(ASCP)
Program Manager

Laura Martin
Editorial Manager

Catherine E.M. Jenkins, ELS
Editor

Kristy L. Leirer, MS
Editor

Lisa M.W. Walker, MS, ELS
Editor

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Lacie Gunnett, BS
Zoetis
USA

Jeffrey L. Watts, PhD, RM(NRCM), M(ASCP)
Zoetis
USA

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Overview of Changes

VET01S-Ed6 replaces the previous edition of the supplement, VET01S-Ed5, published in 2020. The major changes in VET01S-Ed6 are listed below. Other minor or editorial changes were made to the general formatting and to some of the table footnotes and comments. Changes to the tables since the previous edition appear in boldface type. The following are additions or changes unless otherwise noted as a "***deletion***."

- **General:**
  - Harmonized language and common information on methods and QC with CLSI documents M02,[2] the *M02 Disk Diffusion Reading Guide*,[3] M07,[4] and M100[5]
  - Added clinical microbiologists to list of appropriate stakeholders throughout the document
  - Removed veterinary fastidious medium (VFM), which has been replaced with Mueller-Hinton fastidious broth medium with yeast extract (MHF-Y) throughout the document
  - Revised Tables 2A through 2J:
    - Removed comments on dosage regimens used to establish breakpoints (see Appendix D)
    - Moved mastitis breakpoints previously located in Tables 2A through 2E to new tables and revised the body site to "mammary gland":
      - Enterobacterales mastitis breakpoints: moved from Table 2A to 2K
      - *Staphylococcus* spp. mastitis breakpoints: moved from Tables 2C-1 and 2C-2 to 2L
      - *Streptococcus* spp. mastitis breakpoints: moved from Table 2E to 2M
    - Updated human breakpoints in Tables 2A and 2B per recent formatting changes to CLSI document M100,[5] Tables 2:
      - An intermediate (I) value with a ^ indicates agents that have the potential to concentrate in urine in humans. The I^ is for informational use only. The decision to report I^ is best made by each laboratory based on institution-specific guidelines and in consultation with appropriate medical personnel.
      - Added symbol list below Tables 2A and 2B for "^" symbol
- **Summary of CLSI Processes for Establishing Breakpoints and Quality Control Ranges (p. xxiv):**
  - Revised statement on human breakpoints to clarify that they may be useful for some scenarios when no veterinary breakpoints are available
  - Clarified statement on the possibility of a microorganism's susceptibility to an antimicrobial agent to decrease over time

Overview of Changes (Continued)

- **CLSI Veterinary-Specific Breakpoint Additions/Revisions Since January 2021 (p. xxvi):**
  - Added breakpoints for the following drug, organism, and body site combinations for the following animal species:
    - Dogs:
      - Amoxicillin-clavulanate minimal inhibitory concentration (MIC) breakpoints for *Enterococcus* spp. in urinary tract infections (UTIs)
      - Ampicillin MIC breakpoints for *Enterococcus* spp. in skin and soft tissue (SST) infections
      - Ampicillin zone diameter and MIC breakpoints for *Enterococcus* spp. in UTIs
      - Doxycycline MIC breakpoints for *Escherichia coli*
      - Piperacillin-tazobactam zone diameter breakpoints for Enterobacterales in SST infections and UTIs
    - Cats:
      - Amoxicillin-clavulanate MIC breakpoints for *Enterococcus* spp. in UTIs
      - Ampicillin zone diameter and MIC breakpoints for *E. coli* in UTIs
      - Ampicillin zone diameter and MIC breakpoints for *Enterococcus* spp. in UTIs
    - Cattle:
      - Kanamycin-cephalexin zone diameter and MIC breakpoints for *E. coli* in intramammary infections
      - Kanamycin-cephalexin zone diameter and MIC breakpoints for *S. aureus* in intramammary infections
      - Kanamycin-cephalexin zone diameter and MIC breakpoints for coagulase-negative staphylococci (CoNS) in intramammary infections
      - Kanamycin-cephalexin zone diameter and MIC breakpoints for *Streptococcus dysgalactiae* and *Streptococcus uberis* in intramammary infections
      - Pradofloxacin zone diameter and MIC breakpoints for *Pasteurella multocida* in respiratory infections
      - Pradofloxacin zone diameter and MIC breakpoints for *Histophilus somni* in respiratory infections
    - Swine:
      - Pradofloxacin zone diameter and MIC breakpoints for *P. multocida* in respiratory infections
      - Pradofloxacin breakpoints for *Actinobacillus pleuropneumoniae* in respiratory infections

  - Revised footnote a to include the previous edition (VET01S-Ed5)

- **Instructions for Use of Tables:**
  - Section I.C. Test/Report Groups (p. 2):
    - Revised Group B:
      - Revised the Subcommittee on Veterinary Antimicrobial Susceptibility Testing's recommendations on the use of Group B antimicrobial agents
    - Revised Group D:
      - Added statement on the role of MIC values of group D agents
      - ***Deleted*** text on applying interpretive categories determined by breakpoints set for a particular animal species to other animal species

Overview of Changes (Continued)

- Revised Group E:
  - Revised conditions under which group E agents may be used in an extralabel manner
  - Revised statement on the use of group E agents for monitoring antimicrobial resistance patterns or for surveillance programs to indicate that these activities should be performed with guidance from an antimicrobial stewardship program and added reference to the American Veterinary Medical Association

- Section I.D. Selective Reporting (p. 3):
  - In second paragraph, revised mentions of agents in groups A, C, and D to read, "groups A, B, C, and E"
  - Revised example of regulatory agencies or authorities in some countries prohibiting use of antimicrobial agents to clarify the role of US regulations and updated reference to cite the US Code of Federal Regulations
  - Added paragraph including special considerations that should be taken when agents in group D are selectively reported

- Section II. Breakpoints and Interpretive Category Definitions (p. 4):
  - Intermediate (I) definition:
    - Revised portion of NOTE 1 to clarify that the intermediate category includes a buffer zone for inherent variability in test methods
    - Added NOTE 2 explaining the "^" symbol for human breakpoint intermediate values in Tables 2A and 2B

- Section III. Reporting Results (p. 6):
  - Section A, Organisms Included in Table 2:
    - Removed "when possible" from text regarding the need to provide an interpretive category result on an MIC report
    - Added statement on the usefulness of an MIC when no breakpoints and interpretive categories are available
    - Changed example from "tigecycline" to "apramycin"
    - Referred users to CLSI document VET09[6] for information on applying a species-specific breakpoint to a different bacterial species, indication, infection site, or animal species than the bacteria, indication, infection site, or animal species for which a breakpoint is approved
  - Section B, Organisms Excluded From Table 2:
    - Added reasons some organisms might be excluded
    - Referred users to CLSI document VET09[6] for information to help determine when use of breakpoints for another organism in a closely related group may be considered

- Section IV. Therapy-Related Comments (p. 8):
  - Revised examples of therapy-related comments that may be appropriate to include on the patient report, eg:
    - Noting that cases of uncomplicated UTIs should be treated with ß-lactams such as ampicillin, amoxicillin, or penicillin

Overview of Changes (Continued)

        - Indicating recommended and alternative therapies for serious non-UTI enterococcal infections, eg, bacteremia
    - Revised paragraph about dosage regimens, which are now located only in Appendix D, to clarify information and recommendations (eg, the appropriate manner of sharing dosage regimens with clinicians)

- Section VI. Development of Resistance and Testing of Repeat Isolates (p. 9):
    - Changed "veterinary microbiologist" to "clinical microbiologist"

- Section VIII. Routine, Supplemental, Screening, Surrogate Agent, and Equivalent Agent Testing to Determine Susceptibility and Resistance to Antimicrobial Agents (p. 9):
    - Removed "and chlortetracycline" from the example in the equivalent agent test category
    - Revised table title to read, "Supplemental Tests – Required for Reporting Clinical Results"
    - Revised table title to read, "Supplemental Tests – Optional for Reporting Clinical Results"
    - Added clindamycin row to Surrogate Agent Tests table and clarified that broth microdilution or disk diffusion with clindamycin and erythromycin tested together detect inducible clindamycin resistance that predicts inducible lincosamide (ie, clindamycin, lincomycin, and pirlimycin) resistance

- **Table 1. Antimicrobial Agents That Could Be Considered for Routine Testing by Veterinary Microbiology Laboratories:**
    - Group A – Veterinary-Specific Breakpoints (p. 18):
        - Added kanamycin-cephalexin for bovine mastitis
        - Added pradofloxacin for swine and cattle

    - Group C – Human Breakpoints (p. 20):
        - ***Deleted*** cephalexin for cats

    - Group D – Only QC Ranges Available (Breakpoints Not Established) (p. 21):
        - ***Deleted*** kanamycin-cephalexin for bovine mastitis

    - Table 1 NOTEs and footnotes:
        - Revised NOTE 4 to include clinical microbiologists and to align the Group E description with the Instructions for Use of Tables, ie, compounds listed in Group E may be used in an extralabel manner in the United States, per regulations promulgated from the Animal Medicinal Drug Use Clarification Act of 1994 (p. 22)
        - Revised NOTE 6 (p. 22):
            - Revised beginning of note to describe Group B agents as secondary choices to consider only when resistance is detected for agents in Group A or when there are no other reasonable alternatives
            - ***Deleted*** phrase "drugs of last resort"
        - Revised NOTE 7 to indicate that table of commercial disks availability was moved to the new Appendix G (p. 22)
        - ***Deleted*** "in lactating dairy cattle" from footnote b (p. 18)

Overview of Changes (Continued)

- Revised footnote e to indicate that results of ampicillin testing can be used to predict results for amoxicillin (p. 18)
- Revised footnote f to indicate that clindamycin is used as a surrogate to predict results for susceptibility to lincomycin (p. 18)
- ***Deleted*** chlortetracycline from footnote g (p. 19)

- **Table 2A. Zone Diameter and MIC Breakpoints for Enterobacterales:**
  - General comments:
    - Revised general comment (3) to refer users to Appendix D for information about dosage regimens used to establish breakpoints (p. 27)
    - Added general comment (4) explaining the "^" symbol for human breakpoint intermediate values in Tables 2A and 2B (p. 27)

  - Veterinary-specific breakpoints:
    - Added canine-specific doxycycline MIC breakpoints and comment for *E. coli* (p. 29)
    - Added canine-specific piperacillin-tazobactam zone diameter breakpoints for Enterobacterales in SST infections and UTIs (p. 29)
    - Added feline-specific ampicillin zone diameter and MIC susceptible-only breakpoints for *E. coli* in UTIs (p. 30)

  - Comments on veterinary-specific breakpoints:
    - Added comment (9) to feline-specific amoxicillin-clavulanate breakpoints for *E. coli* in UTIs noting that breakpoints were derived from published literature in which amoxicillin-clavulanate was administered to nonazotemic cats (p. 30)

  - Human breakpoints (gray-shaded):
    - Added human (gray-shaded) meropenem zone diameter and MIC breakpoints for Enterobacterales (p. 37)
    - Revised human (gray-shaded) breakpoints:
      - Added "^" after the intermediate interpretive category value and comment(s) for:
        - Amikacin (p. 32)
        - Amoxicillin-clavulanate (p. 32)
        - Ampicillin (p. 33)
        - Ceftazidime (p. 35)
        - Gentamicin (p. 36)
        - Kanamycin (p. 36)
        - Imipenem (p. 37)
        - Levofloxacin (p. 37)
        - Streptomycin (p. 38)
    - ***Deleted*** human (gray-shaded) piperacillin-tazobactam zone diameter and MIC breakpoints for Enterobacterales

  - Comments and footnotes on human breakpoints (gray-shaded):
    - Added symbol list for "^" symbol (p. 38)
    - Added footnote d clarifying relevance of comments on human breakpoints (p. 33)

Overview of Changes (Continued)

- **Table 2B. Zone Diameter and MIC Breakpoints for *Pseudomonas aeruginosa:***
  - General comments:
    - Revised general comment (4) to refer users to Appendix D for information about dosage regimens used to establish breakpoints (p. 40)
    - Added general comment (5) explaining the "^" symbol for human breakpoints in Tables 2A and 2B (p. 41)
  - Human breakpoints (gray-shaded):
    - Added human (gray-shaded) meropenem zone diameter and MIC breakpoints for *P. aeruginosa* (p. 42)
    - Revised human (gray-shaded) breakpoints:
      - Added "^" after the intermediate interpretive category value and comment(s) for (p. 42):
        - Amikacin
        - Ceftazidime
        - Gentamicin
        - Imipenem
        - Levofloxacin
        - Piperacillin-tazobactam
  - Comments and footnotes on human breakpoints (gray-shaded):
    - Added symbol list for "^" symbol (p. 42)

- **Table 2C-1. Zone Diameter and MIC Breakpoints for *Staphylococcus* spp. for ß-Lactams and ß-Lactam Combination Agents:**
  - Testing conditions:
    - ***Deleted*** footnote a for *Staphylococcus hyicus* when trimethoprim and the sulfonamides are tested by broth microdilution (ie, not applicable to Table 2C-1 for β-lactams and β-lactam combination agents)
  - General comments:
    - Revised general comment (4) to refer users to Appendix D for information about dosage regimens used to establish breakpoints (p. 45)
    - Revised general comment (6) (p. 45):
      - Revised beginning of comment to note that tests for *mecA* and PBP2a are the most definitive tests for detection of methicillin (oxacillin) resistance for *Staphylococcus* spp. and to explain the conditions under which isolates should be reported as methicillin (oxacillin)-resistant
      - In the Methods for Detection of Methicillin (Oxacillin)-Resistant *Staphylococcus* spp. table, revised "Other *Staphylococcus* spp. (not listed above)" to read, "Other *Staphylococcus* spp. (not listed above or not identified to the species level)" and added footnote a, including a supporting reference, for isolates from serious infections

Overview of Changes (Continued)

- Comments and footnotes on human breakpoints (gray-shaded):
  - Revised "BMHA" to read, "MHA with 5% sheep blood" in comment (15) (p. 48)
  - Added comment (17) to human (gray-shaded) oxacillin zone diameter and MIC breakpoints for *Staphylococcus epidermidis, S. pseudintermedius* and *S. schleiferi,* and Other *Staphylococcus* spp., excluding *S. aureus, S. lugdunensis, S. epidermidis, S. pseudintermedius,* and *S. schleiferi* explaining the use of VET01S breakpoints compared with revised breakpoints published in CLSI document M100[5] (p. 49)
  - Added footnote c clarifying relevance of comments on human breakpoints (p. 46)
  - ***Deleted*** footnote e regarding isolates of "other *Staphylococcus* spp.," as this information is incorporated into comment (18)

- Comments on veterinary-specific breakpoints:
  - Revised comment (22) for canine-specific ampicillin MIC breakpoints for *S. pseudintermedius* to indicate that results of ampicillin susceptibility tests should be used to predict the activity of aminopenicillins among non-β-lactamase-producing staphylococci (p. 51)
  - Added comment (23) for equine-specific penicillin G MIC breakpoints for *Staphylococcus* spp. regarding confirmation of susceptible isolates (p. 52)

- **Table 2C-2. Zone Diameter and MIC Breakpoints for *Staphylococcus* spp. for Non-ß-Lactams:**
  - Routine QC recommendations:
    - ***Deleted*** *E. coli* ATCC® 35218

  - General comments:
    - Revised general comment (5) to refer users to Appendix D for information about dosage regimens used to establish breakpoints (p. 55)

  - Comments on veterinary-specific breakpoints:
    - Revised beginning of comment (9) for canine-specific tetracycline zone diameter and MIC breakpoints for *Staphylococcus* spp. to indicate that results of tetracycline testing can be used to predict results for oxytetracycline, doxycycline, and minocycline (p. 56)

  - Human breakpoints (gray-shaded):
    - Added human (gray-shaded) linezolid zone diameter and MIC breakpoints and comment for all staphylococci (p. 59)

  - Footnotes on human breakpoints (gray-shaded):
    - Added footnote f clarifying relevance of comments on human breakpoints (p. 58)

- **Table 2D. Zone Diameter and MIC Breakpoints for *Enterococcus* spp.:**
  - General comments:
    - Added linezolid to list in general comment (2) of antimicrobial agents that may have trailing growth, making end-point determination difficult (p. 64)
    - Revised general comment (4) to specify conditions under which enterococci may be susceptible to synergistic killing by penicillin or ampicillin (p. 64)

Overview of Changes (Continued)

- Revised general comment (5) to note the animal species with species-specific breakpoints and to discuss appropriate use of human data (p. 65)
- Added general comment (6) to refer users to Appendix D for information about dosage regimens used to establish breakpoints (p. 65)

– Veterinary-specific breakpoints:
- Added canine-specific amoxicillin-clavulanate MIC breakpoints for *Enterococcus* spp. in UTIs (p. 66)
- Added canine-specific ampicillin MIC breakpoints and comment for *Enterococcus* spp. in SST infections (p. 66)
- Added canine-specific ampicillin zone diameter and MIC breakpoints and comment for *Enterococcus* spp. in UTIs (p. 66)
- Added feline-specific amoxicillin-clavulanate MIC breakpoints and comment for *Enterococcus* spp. in UTIs (p. 66)
- Added feline-specific ampicillin zone diameter and MIC breakpoints for *Enterococcus* spp. in UTIs (p. 66)

– Human breakpoints (gray-shaded):
- Added human (gray-shaded) linezolid zone diameter and MIC breakpoints and comment for *Enterococcus* spp. (p. 68)
- Moved human (gray-shaded) penicillin zone diameter and MIC breakpoints to be in alphabetical order (p. 69)

– Comments and footnotes on human breakpoints (gray-shaded):
- Revised ***Rx*** comment (11) for ampicillin and penicillin (p. 67):
  - Revised beginning to indicate recommended and alternative therapies for serious non-UTI enterococcal infections
  - ***Deleted*** text on low-level penicillin or ampicillin resistance that preceded reference to Table 7G
- Added footnote c clarifying relevance of comments on human breakpoints (p. 67)

- **Table 2E. Zone Diameter and MIC Breakpoints for *Streptococcus* spp.:**
  – General comments:
    - Revised general comment (1) to clarify the zone that should be measured (p. 72)
    - Revised general comment (2) to apply to β-hemolytic streptococci and pneumococci and added information for pneumococci when trimethoprim and the sulfonamides are tested (p. 72)
    - Revised general comment (4) to refer users to Appendix D for information about dosage regimens used to establish breakpoints (p. 73)

  – Veterinary-specific breakpoints:
    - Added canine-specific amikacin MIC breakpoints for *Streptococcus* spp. that were removed from VET01S-Ed5 (p. 73)

Overview of Changes (Continued)

- Comments on veterinary-specific breakpoints:
  - Revised comment (5) for canine-specific ampicillin MIC susceptible-only breakpoint for *Streptococcus* spp. in SST infections to indicate that results of ampicillin testing can be used to predict results for amoxicillin (p. 73)
  - Revised comment (12) for porcine-specific tetracycline MIC breakpoints for *Streptococcus suis* in respiratory infections to indicate that results of tetracycline testing can be used to predict results for oxytetracycline (p. 76)

- Footnotes on human breakpoints (gray-shaded):
  - Added footnote f clarifying relevance of comments on human breakpoints (p. 77)

- **Table 2F. Zone Diameter and MIC Breakpoints for *Bordetella bronchiseptica*:**
  - General comments:
    - Revised general comment (2) to refer users to Appendix D for information about dosage regimens used to establish breakpoints (p. 84)

  - Comments on veterinary-specific breakpoints:
    - Revised comment (3) for porcine-specific ampicillin MIC breakpoints for *Bordetella bronchiseptica* in respiratory infections to indicate that results of ampicillin testing can be used to predict results for amoxicillin (p. 85)

- **Table 2G. Zone Diameter and MIC Breakpoints for *Mannheimia haemolytica*:**
  - General comments:
    - Revised general comment (2) to refer users to Appendix D for information about dosage regimens used to establish breakpoints (p. 86)

  - Comments on veterinary-specific breakpoints:
    - Revised comment (3) for bovine-specific tetracycline MIC breakpoints for *M. haemolytica* in respiratory infections to indicate that results of tetracycline testing can be used to predict results for oxytetracycline (p. 87)

- **Table 2H. Zone Diameter and MIC Breakpoints for *Pasteurella multocida*:**
  - General comments:
    - Updated general comment (2) to refer users to Appendix D for information about dosage regimens used to establish breakpoints (p. 88)

  - Veterinary-specific breakpoints:
    - Added bovine-specific pradofloxacin zone diameter and MIC breakpoints for *P. multocida* in respiratory infections (p. 89)
    - Added porcine-specific pradofloxacin zone diameter and MIC breakpoints for *P. multocida* in respiratory infections (p. 90)

  - Comments on veterinary-specific breakpoints:
    - Revised comment (4) for bovine-specific and porcine-specific tetracycline MIC breakpoints for *P. multocida* in respiratory infections to indicate that results of tetracycline testing can be used to predict results for oxytetracycline (p. 89)

Overview of Changes (Continued)

    - Revised comment (5) for porcine-specific ampicillin MIC breakpoints for *P. multocida* in respiratory infections to indicate that results of ampicillin testing can be used to predict results for amoxicillin (p. 90)

- **Table 2I. Zone Diameter and MIC Breakpoints for *Actinobacillus* spp.:**
  - General:
    - Revised "*Actinobacillus pleuropneumoniae*" in table title to "*Actinobacillus* spp." and added "Organism" column
  - Testing conditions:
    - ***Deleted*** veterinary fastidious medium
  - General comments:
    - Revised general comment (3) to refer users to Appendix D for information about dosage regimens used to establish breakpoints (p. 92)
  - Veterinary-specific breakpoints:
    - Added porcine-specific pradofloxacin zone diameter and MIC susceptible-only breakpoints for *A. pleuropneumoniae* in respiratory infections (p. 93)
  - Comments on veterinary-specific breakpoints:
    - Revised comment (4) for porcine-specific ampicillin MIC breakpoints for *A. pleuropneumoniae* in respiratory infections to indicate that results of ampicillin testing can be used to predict results for amoxicillin (p. 93)
    - Revised comment (5) for porcine-specific tetracycline MIC breakpoints for *A. pleuropneumoniae* in respiratory infections to indicate that results of tetracycline testing can be used to predict results for oxytetracycline (p. 93)

- **Table 2J. Zone Diameter and MIC Breakpoints for *Histophilus somni*:**
  - Testing conditions:
    - ***Deleted*** veterinary fastidious medium
  - General comments:
    - Revised general comment (3) to refer users to Appendix D for information about dosage regimens used to establish breakpoints (p. 96)
  - Veterinary-specific breakpoints:
    - Added bovine-specific pradofloxacin zone diameter and MIC breakpoints for *H. somni* in respiratory infections (p. 97)
  - Comments on veterinary-specific breakpoints:
    - Revised comment (4) for bovine-specific tetracycline MIC breakpoints for *H. somni* in respiratory infections to indicate that results of tetracycline testing can be used to predict results for oxytetracycline (p. 97)

Overview of Changes (Continued)

- **Table 2K. Zone Diameter and MIC Mastitis Breakpoints for Enterobacterales:**
  - General comments:
    - Revised general comment (2) to recommend that only drugs with mastitis-specific breakpoints be reported when mastitis pathogens are tested (p. 98)
    - Revised general comment (3) noting differences because of anatomical site and primary route of drug administration (ie, intramammary infusion) compared with oral (PO), intravenous (IV), or intramuscular (IM) routes and referring users to Appendix D for information about dosage regimens expected to achieve milk drug exposures and, when appropriate, used to establish breakpoints (p. 98)
  - Veterinary-specific breakpoints:
    - Added bovine-specific kanamycin-cephalexin zone diameter and MIC breakpoints for *E. coli* in mastitis (p. 99)
    - Moved mastitis breakpoints previously located in Table 2A to Table 2K (p. 99)
  - Comments on veterinary-specific breakpoints:
    - Added comment (5) noting ESBL-positive isolates should be reported as ceftiofur resistant (p. 99)

- **Table 2L. Zone Diameter and MIC Mastitis (Intramammary Infection) Breakpoints for *Staphylococcus* spp.:**
  - Testing conditions:
    - ***Deleted*** footnote a for *Staphylococcus hyicus* when trimethoprim and the sulfonamides are tested by broth microdilution (ie, not applicable to Table 2L for β-lactams and β-lactam combination agents)
  - General comments:
    - Revised general comment (2) noting differences because of anatomical site and primary route of drug administration (ie, intramammary infusion) compared with PO, IV, or IM routes and referring users to Appendix D for information about dosage regimens expected to achieve milk drug exposures and, when appropriate, used to establish breakpoints (p. 100)
    - Added general comment (3) noting additional considerations for interpreting antimicrobial susceptibility testing results for *S. aureus* isolated from bovine mastitis (p. 100)
    - Revised general comment (5) to explain table organization of human (gray-shaded) breakpoints and bovine-specific breakpoints in mastitis and to note that breakpoints were set based on the approved route of administration (p. 101)
    - Revised general comment (7):
      - Revised beginning of comment to note that tests for *mecA* and PBP2a are the most definitive tests for detection of methicillin (oxacillin) resistance for *Staphylococcus* spp. and to explain the conditions under which isolates should be reported as methicillin (oxacillin)-resistant (p. 101)
      - In the Methods for Detection of Methicillin (Oxacillin)-Resistant *Staphylococcus* spp. table, revised "Other *Staphylococcus* spp. (not listed above)" to read, "Other *Staphylococcus* spp. (not listed above or not identified to the species level)" and added footnote a, including a supporting reference, for isolates from serious infections (p. 102)

Overview of Changes (Continued)

- Veterinary-specific breakpoints:
  - Added bovine-specific kanamycin-cephalexin zone diameter and MIC breakpoints for *S. aureus* and CoNS in mastitis (p. 107)
  - Moved mastitis breakpoints previously located in Tables 2C-1 and 2C-2 to Table 2L (p. 107)

- Comments on veterinary-specific breakpoints:
  - Added comment (23) noting MRSA should be reported as ceftiofur resistant (p. 107)

- Comments and footnotes on human breakpoints (gray-shaded):
  - Revised comment (14) to note that cloxacillin is a common mastitis intramammary product (p. 103)
  - Revised "BMHA" to read, "MHA with 5% sheep blood" in comment (16) (p. 104)
  - Added comment (18) to human (gray-shaded) oxacillin zone diameter and MIC breakpoints for *Staphylococcus epidermidis, S. pseudintermedius* and *S. schleiferi,* and other *Staphylococcus* spp., excluding *S. aureus, S. lugdunensis, S. epidermidis, S. pseudintermedius,* and *S. schleiferi* explaining the use of VET01S breakpoints compared with revised breakpoints published in CLSI document M100[5] (p. 105)
  - Added footnote c clarifying relevance of comments on human breakpoints (p. 102)
  - ***Deleted*** footnote e regarding isolates of "other Staphylococcus spp.," as this information is incorporated into comment (19)

- **Table 2M. Zone Diameter and MIC Mastitis (Intramammary Infection) Breakpoints for *Streptococcus* spp.:**
  - General comments:
    - Revised general comment (1) to clarify the zone that should be measured (p. 110)
    - Revised general comment (3) noting differences because of anatomical site and primary route of drug administration (ie, intramammary infusion) compared with PO, IV, or IM routes and referring users to Appendix D for information about dosage regimens expected to achieve milk drug exposures and, when appropriate, used to establish breakpoints (p. 110)

  - Veterinary-specific breakpoints:
    - Added bovine-specific kanamycin-cephalexin zone diameter and MIC breakpoints for *S. dysgalactiae* and *S. uberis* in mastitis (p. 111)
    - Revised penicillin-novobiocin antimicrobial agent class or subclass to "combination penicillinase-labile penicillin and aminocoumarin" for *Streptococcus agalactiae*, *S. dysgalactiae,* and *S. uberis* in mastitis (p. 111)
    - Moved mastitis breakpoints previously located in Table 2E to Table 2M (p. 111)

- **Table 4A. Zone Diameter QC Ranges for Nonfastidious Organisms (p. 114):**
  - Revised amikacin QC ranges for *P. aeruginosa* ATCC® 27853 to read, "20-26 mm"

- **Table 5A. MIC QC Ranges for Nonfastidious Organisms (p. 126):**
  - Revised amoxicillin-clavulanate QC range upper limit for *Enterococcus faecalis* ATCC® 29212 from "1.0/0.5" to "1/0.5"

Overview of Changes (Continued)

- Revised ceftiofur QC range upper limit for *S. aureus* ATCC® 29213 from "1.0" to "1"
- Revised pirlimycin QC range upper limit for *S. aureus* ATCC® 29213 from "1.0" to "1"

- **Table 5B. MIC QC Ranges for Fastidious Organisms (Broth Dilution Methods) (p. 128):**
  - Revised MIC Testing Conditions for Clinical Isolates and Performance of QC table:
    - Added "ambient air" for *P. multocida* and *M. haemolytica* incubation
    - ***Deleted*** comment for *P. multocida* and *M. haemolytica*
    - ***Deleted*** VFM medium and incubation conditions for *H. somni* and *A. pleuropneumoniae*

  - ***Deleted*** MIC QC ranges for *H. somni* ATCC® 700025 and *A. pleuropneumoniae* ATCC® 27090 in VFM

- **Table 5F. MIC Troubleshooting Guide (p. 136):**
  - Added row for testing *E. coli* ATCC® 35218 and *K. pneumoniae* ATCC® 700603 against various antimicrobial agents (β-lactams) with the resulting MICs too low

  - Added row for testing *S. aureus* ATCC® 29213, *Enterococcus faecalis* ATCC® 29212, and *Streptococcus pneumoniae* ATCC® 49619 against chloramphenicol, clindamycin, erythromycin, and/or tetracycline with the resulting MICs too high

  - Moved row for testing *S. pneumoniae* ATCC® 49619 against various antimicrobial agents with the resulting MICs too low

- **Table 6. Solvents and Diluents for Preparing Stock Solutions of Antimicrobial Agents (p. 140):**
  - Revised footnote g to refer to Appendix G instead of Table 1 for sponsor contact information

- **Table 7F. Tests for Detection of Inducible Clindamycin Resistance in *Staphylococcus* spp., *Streptococcus* spp. B-Hemolytic Group, and *Streptococcus pneumoniae* (p. 154):**
  - Added QC strain in QC recommendations – lot/shipment row for disk diffusion (D-zone test)

  - Revised footnote e to include disk diffusion

- **Table 7G. Tests for Detection of High-Level Aminoglycoside Resistance in *Enterococcus* spp. (Includes Disk Diffusion) (p. 156):**
  - Revised last comment in "Additional testing and reporting" row to specify conditions under which enterococci may be susceptible to synergistic killing by penicillin and ampicillin

- **Appendix A. Suggestions for Confirming Resistant, Intermediate, or Nonsusceptible Antimicrobial Susceptibility Test Results and Organism Identification (p. 158):**
  - Revised footnote d to clarify that as of May 2022, 10 transferable colistin resistance genes are available, *mcr-1* to *mcr-10,* most of them with several subtypes, and added supporting references

Overview of Changes (Continued)

- Added footnote e to describe various results of acquired colistin resistance due to chromosomal mutations and alternative metabolic pathways

- **Appendix B. Intrinsic Resistance (p. 164):**
  - Revised third introductory paragraph to indicate that:
    - When an isolate has known intrinsic resistance to an antimicrobial agent tested, it should be considered resistant regardless of *in vitro* testing results.
    - Intrinsic resistance should not be reported or, if reported, should include a comment to differentiate intrinsic resistance from acquired resistance.

  - B1. Enterobacterales:
    - Added designation of intrinsic resistance for *Hafnia alvei* and polymyxin B and colistin as well as footnote c on *Hafnia paralvei*
    - Revised the comment for *E. coli* regarding intrinsic resistance to β-lactams
    - ***Deleted*** the designation of intrinsic resistance for these organisms and the antimicrobial agent shown:
      - *Enterobacter cloacae* complex and cephalosporins II
      - *Klebsiella* (formerly *Enterobacter*) *aerogenes* and cephalosporins II
      - *Morganella morganii* and ampicillin-sulbactam
      - *Yersinia enterocolitica* and ampicillin-sulbactam

  - B2. Non-Enterobacterales:
    - ***Deleted*** the designation of intrinsic resistance for *Acinetobacter baumannii/Acinetobacter calcoaceticus* complex and cefotaxime

- **Appendix D. Dosage Regimens Used to Establish Susceptible Veterinary-Specific Breakpoints (p. 176):**
  - Added dosage regimens used to establish breakpoints for the following drug, organism, and body site (if specified) combinations for:
    - Dogs:
      - Doxycycline for *E. coli* (Table 2A)
      - Amoxicillin-clavulanate for *Enterococcus* spp. in UTIs (Table 2D)
      - Ampicillin for *Enterococcus* spp. in UTIs and SST infections (Table 2D)
    - Cats:
      - Ampicillin for *E. coli* in UTIs (Table 2A)
      - Amoxicillin-clavulanate for *Enterococcus* spp. in UTIs (Table 2D)
      - Ampicillin for *Enterococcus* spp. in UTIs (Table 2D)
    - Cattle:
      - Pradofloxacin for *P. multocida* and *H. somni* in respiratory infections (Tables 2H and 2J, respectively)
      - Kanamycin-cephalexin for *E. coli, S. aureus,* CoNS, *Streptococcus dysgalactiae,* and *Streptococcus uberis* in mastitis (Tables 2K, 2L, and 2M, respectively)
    - Swine:
      - Pradofloxacin for *P. multocida* and *A. pleuropneumoniae* in respiratory infections (Tables 2H and 2I, respectively)

Overview of Changes (Continued)

- Added supporting reference for dosage regimens used to establish ampicillin breakpoints for respiratory infections in swine for the following organisms:
  - *S. suis* (Table 2E)
  - *B. bronchiseptica* (Table 2F)
  - *P. multocida* (Table 2H)
  - *A. pleuropneumoniae* (Table 2I)

- Revised dosage regimens used to establish veterinary-specific breakpoints for:
  - Cats:
    - Amoxicillin-clavulanate against *E. coli* and *Enterococcus* spp. in UTIs (Tables 2A and 2D, respectively)
  - Cattle:
    - Cefoperazone against *E. coli, S. aureus, Staphylococcus* spp. other than *S. aureus*, *S. agalactiae, S. dysgalactiae*, and *S. uberis* in mastitis (Tables 2K, 2L, and 2M)
    - Ceftiofur against *E. coli, S. aureus, S. agalactiae, S. dysgalactiae*, and *S. uberis* in mastitis (Tables 2K, 2L, and 2M)

- **Appendix E. QC Strains for Antimicrobial Susceptibility Tests (p. 188):**
  - Added "D-zone test negative" comment for *S. aureus* ATCC® BAA-976™
  - Added "D-zone test positive" comment for *S. aureus* ATCC® BAA-977™

- **Appendix F. CLSI Veterinary-Specific Breakpoint Additions/Revision to VET01 Supplements Since 1999 (p. 192):**
  - Added information (ie, antimicrobial agent, organisms, animal species, body site, table number, and supplement edition) for CLSI veterinary-specific breakpoints added or revised in this edition

  - Revised bovine mastitis breakpoint information to reflect placement in new Tables 2K, 2L, and 2M

  - Revised footnote a to note the current edition of the supplement and add the immediate past edition

- **Appendix G. Sources of Antimicrobial Agent Disks (p. 200):**
  - Moved table of commercial disks availability previously located in Table 1 to new Appendix G

  - Moved enrofloxacin and pradofloxacin previously located in Bayer sponsor row to Elanco Animal Health sponsor row

  - ***Deleted*** Bayer sponsor row

Overview of Changes (Continued)

- **Glossary I. Antimicrobial Class and Subclass Designations, Antimicrobial Agents, and Antimicrobial Resistance Mechanisms (p. 202):**
  - Revised resistance mechanisms that previously applied only to the cephalosporin I agents to apply to cephalosporins I through IV and cephamycin
  - Added kanamycin-cephalexin and penicillin-novobiocin to antimicrobial class "others"
  - Moved apramycin from antimicrobial class "aminocyclitols" to "aminoglycosides"
  - Added antimicrobial resistance mechanisms for carbapenems and polymyxins
  - Revised folate pathway antagonists formerly listed as "sulfonamides" to "sulfamethoxazole" and "sulfisoxazole"
  - ***Deleted*** "polymyxin" from antimicrobial subclass of polypeptides and "lipopolysaccharide modification" from resistance mechanisms for polypeptides
  - ***Deleted*** "sometimes" from footnote a

NOTE: The content of this document is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

Summary of CLSI Processes for Establishing Breakpoints and Quality Control Ranges

The Clinical and Laboratory Standards Institute (CLSI) is an international, voluntary, not-for-profit, interdisciplinary, standards-developing, and educational organization accredited by the American National Standards Institute that develops and promotes the use of consensus-developed standards and guidelines within the health care community. These consensus standards and guidelines are developed in an open and consensus-seeking forum to cover critical areas of diagnostic testing and patient health care. CLSI is open to anyone or any organization that has an interest in diagnostic testing and patient care. Information about CLSI is found at www.clsi.org.

The CLSI Subcommittee on Veterinary Antimicrobial Susceptibility Testing reviews data from a variety of sources and studies (eg, *in vitro,* pharmacokinetics-pharmacodynamics, and clinical studies) to establish antimicrobial susceptibility test methods, breakpoints, and QC parameters. The details of the data necessary to establish breakpoints, epidemiological cutoff values, QC parameters, and how the data are presented for evaluation are described in CLSI document VET02.[7]

The subcommittee's goal is to establish veterinary-specific breakpoints to decrease reliance on human breakpoints. However, human breakpoints are still listed in the VET01S Table 2 series, identified with gray-shaded text, allowing comparison of veterinary-specific and human breakpoints. Human breakpoints **may be useful for some scenarios** when there are no veterinary breakpoints available.

Over time, a microorganism's susceptibility to an antimicrobial agent may decrease, resulting in a **decrease in predicted** clinical **success**. In addition, microbiological methods and QC parameters may be refined to ensure more accurate and better performance of susceptibility test methods. Because of these types of changes, CLSI continually monitors and updates information in its documents. Although CLSI standards and guidelines are developed using the most current information available at the time, the field of science and medicine is always changing; therefore, standards and guidelines should be used in conjunction with clinical judgment, current knowledge, and clinically relevant laboratory test results to guide patient treatment.

Additional information, updates, and changes in this document are found in the meeting summary minutes of the Subcommittee on Veterinary Antimicrobial Susceptibility Testing at www.clsi.org.

CLSI Reference Methods vs Commercial Methods and CLSI vs Regulatory Authority

It is important for users of VET01[1] and VET01S to recognize that the standard methods described in CLSI documents are reference methods. These methods may be used for routine antimicrobial susceptibility testing of patient isolates. CLSI recognizes that commercial susceptibility testing devices are commonly used by veterinary diagnostic laboratories. Commercial testing devices used in veterinary medicine may not have demonstrated that test results from such systems are substantially equivalent to those generated using reference methods. For example, the US Food and Drug Administration does not have preapproval or regulatory clearance requirements for use of commercial testing devices for veterinary isolates. Manufacturers of commercial testing devices are expected to validate their methods against CLSI reference methods, but CLSI does not evaluate these data. Laboratories should follow the manufacturer's instructions for quality assurance and quality control testing. The laboratory is responsible for ensuring that the performance of commercial test systems has been validated against the reference method(s).

Currently, there are no regulations that apply to veterinary laboratories regarding susceptibility testing. Veterinary-specific breakpoints are not set by regulatory agencies but have been developed and approved solely by the CLSI Subcommittee on Veterinary Antimicrobial Susceptibility Testing. The guidelines used by CLSI to evaluate data and determine breakpoints and epidemiological cutoff values are outlined in CLSI document VET02.[7]

CLSI proactively evaluates the need for changing breakpoints. Following a decision by CLSI to change an existing clinical breakpoint, a delay of one or more years may be needed if a breakpoint and interpretive category change is to be implemented by a device manufacturer. Each laboratory should check with the manufacturer of its commercial susceptibility testing device for additional information on the breakpoints and interpretive categories used in its system's software. Following discussions with appropriate stakeholders (eg, veterinarians, infectious diseases practitioners, **clinical microbiologists,** clinical pharmacologists, and antimicrobial stewardship teams, if available), newly approved or revised breakpoints may be implemented by veterinary diagnostic laboratories. If approved by CLSI, new or revised breakpoints for terrestrial animals will be published in this supplement and for aquatic animals in CLSI document VET04.[8]

CLSI Veterinary-Specific Breakpoint Additions/Revisions Since January 2021[a]

Antimicrobial Agent	Table	Organisms	Animal Species	Body Site	Data Source Presentation
Amoxicillin-clavulanate	2D	*Enterococcus* spp.	Dogs	UTI	GWG (September 2021)
Amoxicillin-clavulanate	2D	*Enterococcus* spp.	Cats	UTI	GWG (September 2021)
Ampicillin	2D	*Enterococcus* spp.	Dogs	SST	GWG (September 2021)
Ampicillin	2D	*Enterococcus* spp.	Dogs	UTI	GWG (September 2021)
Ampicillin	2A	*E. coli*	Cats	UTI	GWG (February 2021)
Ampicillin	2D	*Enterococcus* spp.	Cats	UTI	GWG (September 2021)
Doxycycline	2A	*E. coli*	Dogs	N/A	GWG (February 2021)
Kanamycin-cephalexin	2K	*E. coli*	Cattle	Mammary gland	BMIC WG (February 2021)
Kanamycin-cephalexin	2L	*S. aureus*	Cattle	Mammary gland	BMIC WG (February 2021)
Kanamycin-cephalexin	2L	CoNS	Cattle	Mammary gland	BMIC WG (February 2021)
Kanamycin-cephalexin	2M	*S. dysgalactiae* *S. uberis*	Cattle	Mammary gland	BMIC WG (February 2021)
Piperacillin-tazobactam	2A	Enterobacterales	Dogs	SST, UTI	VET01 Editorial WG (April 2022)[b]
Pradofloxacin	2H	*Pasteurella multocida*	Cattle	Resp	Sponsor (September 2021)
Pradofloxacin	2H	*P. multocida*	Swine	Resp	Sponsor (September 2021)
Pradofloxacin	2I	*Actinobacillus pleuropneumoniae*	Swine	Resp	Sponsor (September 2021)
Pradofloxacin	2J	*Histophilus somni*	Cattle	Resp	Sponsor (September 2021)

Abbreviations: BMIC WG, Bovine Mastitis Interpretive Criteria Working Group; CoNS, coagulase-negative staphylococci; GWG, Generic Drug Working Group; N/A, not applicable; resp, respiratory; SST, skin and soft tissue; UTI, urinary tract infection.

[a] For breakpoint additions/revisions since 1999, see Appendix F. Past editions of the standard (with breakpoint tables included) and supplement include: M31-A (June 1999), M31-A2 (May 2002), M31-S1 (May 2004), VET01-A3 (February 2008), VET01-S2 (July 2013), VET01S, 3rd ed. (June 2015), VET08, 4th ed. (June 2018), **and VET01S-Ed5 (October 2020).**

[b] Approved by electronic vote of the Subcommittee on Veterinary Antimicrobial Susceptibility Testing 6-14 April 2022.

Subcommittee on Veterinary Antimicrobial Susceptibility Testing Mission Statement and Responsibilities

Mission Statement:

Develop and promote performance standards, breakpoints, and interpretive categories for *in vitro* antimicrobial susceptibility testing of bacteria isolated from animals.

Responsibilities:

The Subcommittee on Veterinary Antimicrobial Susceptibility Testing is composed of representatives from the professions, government, and industry, including microbiology laboratories, government agencies, health care providers and educators, and pharmaceutical and diagnostic microbiology industries. Using the CLSI voluntary consensus process, the subcommittee develops standards that promote accurate antimicrobial susceptibility testing and appropriate reporting. Responsibilities of the Subcommittee on Veterinary Antimicrobial Susceptibility Testing include:

- Developing standard reference methods for antimicrobial susceptibility tests
- Providing quality control parameters for standard test methods
- Establishing breakpoints and interpretive categories for the results of standard antimicrobial susceptibility tests performed on veterinary pathogens
- Providing suggestions for testing and reporting strategies that are clinically relevant and cost-effective
- Continually refining standards through development of new or revised methods, breakpoints, interpretive categories, and quality control parameters
- Educating users through multimedia communication of standards and guidelines
- Fostering a dialogue with users of these methods and those who apply them

The ultimate purpose of the subcommittee's mission is to provide useful information to enable veterinary diagnostic laboratories to assist the clinician in the selection of appropriate antimicrobial therapy for patient care. The standards and guidelines are meant to be comprehensive and to include all antimicrobial agents for which the data meet established CLSI guidelines. The values that guide this mission are quality, accuracy, fairness, timeliness, teamwork, consensus, and trust.

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Instructions for Use of Tables

These instructions apply to:

- **Table 1:** suggested groupings of antimicrobial agents that could be considered for routine testing and reporting by microbiology laboratories. Placement of antimicrobial agents in Table 1 is either based on approval by relevant regulatory organizations or on use consistent with good clinical practice.

- **Tables 2A through 2M:** tables for each organism group that contain:
  - Recommended testing conditions
  - Routine QC recommendations (also see Chapter 8 in VET01[1])
  - General comments for testing the organism group and specific comments for testing agent-organism combinations
  - Suggested agents that could be considered for routine testing and reporting by veterinary microbiology laboratories, as specified in Table 1 (test/report groups A, B, C, D, E)
  - Zone diameter and minimal inhibitory concentration (MIC) breakpoints

- **Tables 3 through 5:** tables for acceptable QC organisms, sources, and acceptable result ranges

- **Table 6:** table of solvents and diluents for preparing stock solutions of antimicrobial agents

- **Tables 7A through 7G:** tables describing tests to detect resistance types in specific organisms or organism groups (also see Chapter 7 in VET01[1])

I. Selecting Antimicrobial Agents for Testing and Reporting

A. Appropriate Agents for Routine Testing

Selecting the most appropriate antimicrobial agents to test and report is a decision best made by each laboratory in consultation with veterinarians, infectious diseases practitioners, **clinical microbiologists,** clinical pharmacologists, and antimicrobial stewardship teams, if available. The recommendations for each organism group include antimicrobial agents that show acceptable *in vitro* test performance. Considerations in the assignment of antimicrobial agents to specific test/report groups include clinical efficacy, prevalence of resistance, minimizing emergence of resistance, cost, regulatory agency–approved clinical indications for use, and current consensus recommendations for first-choice and alternative agents. Tests of selected agents may be useful for infection control and/or monitoring purposes.

B. Equivalent Agents

Antimicrobial agents listed together in a single box are agents for which interpretive categories (susceptible, intermediate, or resistant) and clinical efficacy are similar. Within each box, an “or” between agents indicates agents for which cross-resistance