

Center for Veterinary Medicine Office of Research

David G. White, Ph.D.
Director
Office of Research
Center for Veterinary Medicine

Center for
Veterinary Medicine
Department of Health and Human Services
Public Health Service
Food and Drug Administration

8401 Muirkirk Road

CVM Research

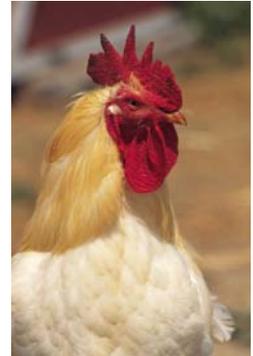
- **Maintain a strong science base**
 - Accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC)
 - GLP compliant
 - Quality Assurance unit
 - OR Research Manual
- **Answers CVM needs**
 - Public and animal health mission
 - Resolves evolving FDA issues
 - Provide scientific foundation to establish solid regulatory policy



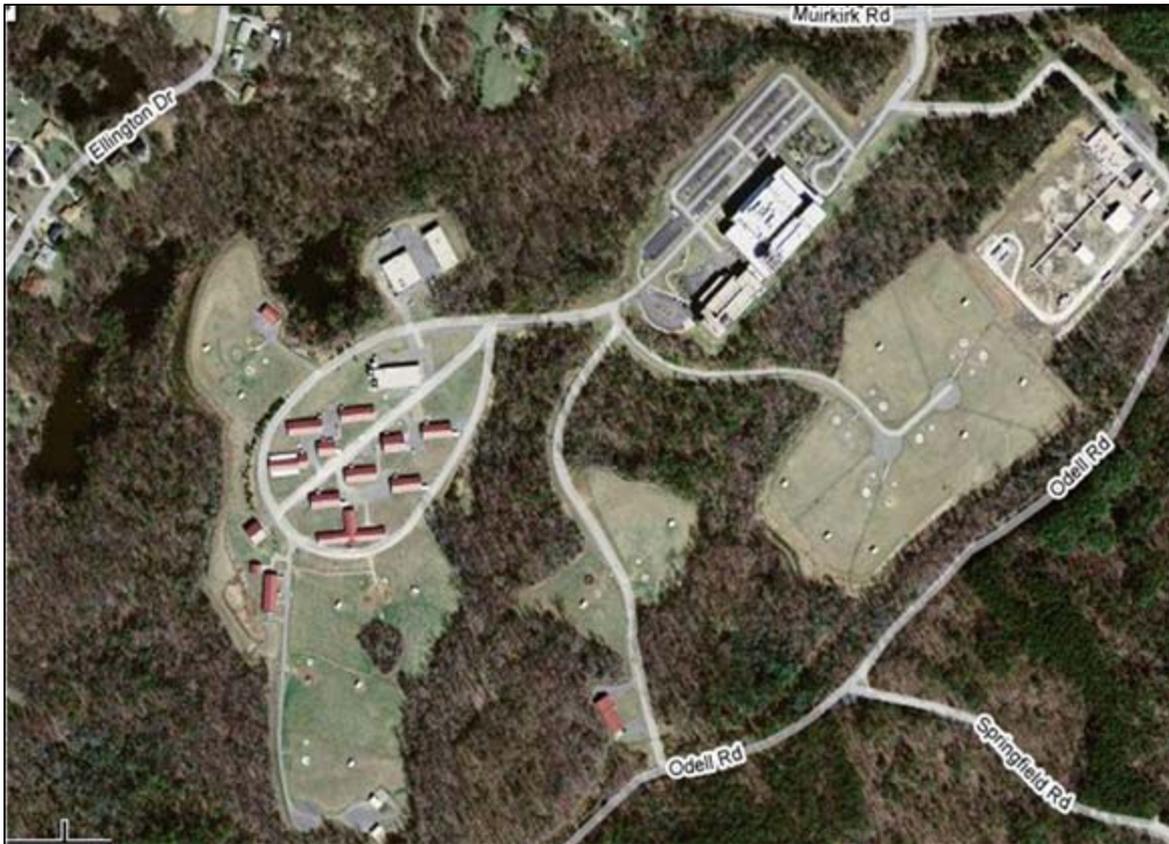
To conduct research to ensure public health, the safety of animal health products and the safety of animal feed

CVM Research: a Focus on Animal and Public Health Outcomes

1. Veterinary Product Efficacy/Safety
 - I. Nanotechnology
 - II. GE Animals
2. Animal Product/Food Safety
3. Aquaculture Program
4. 'Omics' Related Research and Biomarkers
5. Method Validation for Veterinary Drug Approval
6. Method Development for Drug Residues
7. Replacement of Obsolete Regulatory Methods
8. Methods for Contaminants in Animal Feeds
9. NARMS and PulseNet
10. Animal Feed Safety
11. Antimicrobial Resistance Mechanisms
12. Melamine Research
13. **Veterinary Laboratory Response Network (Vet-LRN)**



CVM's Office of Research (OR)



- >165 acres
- 8401 Muirkirk Road
- About 70 staff
- Large-animal housing and surgery suites
- Specialized laboratories
- Aquaculture
- Pastures
- Feed mixing facility
- Quarantine facility

OR Capabilities

- Research programs
 - Food and companion animals
 - Animal and public health
- Specialized and unique facilities/instruments
- Diverse scientific backgrounds
 - Training
 - Assistance for drug reviews
- Leveraging / Collaborations
 - CFSAN/ORR/CDRH/NCTR
 - USDA, CDC
 - Academia
 - International



The research staff at CVM/OR conduct studies to support both pre- and post-marketing activities by providing information to aid CVM scientists in the review and decision-making process

Large Animal Research Facilities



Milk and meat safety



Antimicrobial resistance



Aquaculture research



Biomarker research



Cardiovascular disease research (CDRH)

Office of Research

- Residue Chemistry
 - Dr. Phil Kijak, Director

- Animal Research
 - Dr. Jeff Ward, Director

- Animal and Food Microbiology
 - Dr. Mark Rasmussen, Director

- NARMS
 - Dr. Patrick McDermott, Director
 - Dr. Heather Green Tate, Coordinator

- Vet-LRN
 - Dr. Renate Reimschuessel,
Program Director
 - Sarah Yachetti



OR Subject Expertise

Animal/Dairy/Food Science

Chemistry/ Biochemistry

Biology/Microbiology/Molecular Biology

Epidemiology

Immunology

Pharmacology

Pathology

Toxicology

Veterinary Medicine



Research Priorities



Identify research needs with pre-and post market CVM offices

- ONADE
- OS&C, OMUMS
- Other Center's needs
and Agency programs

Three Year Plan

- Internal Prioritization of research
- Prepared by OR
- Center Management Team (CMT)
reviews & approves



Center for Veterinary Medicine (CVM)

Three-Year Research Plan



Should we do it?

CVM Research Prioritization

1. Communicate
2. Score each
3. Prioritize
4. Communicate

Prioritization factors

- Mandates**
- Congress
 - Administration
 - Agency
 - Center
 - Stakeholder interest
 - Impact on policy and regulation
 - CVM/OR specialty

- Benefits Analysis**
- Public & animal health impact
 - Policy refinement
 - Benefit to stakeholder(s)
 - Resource savings
 - Enhance review, compliance
 - Increased research capacity
 - Prevention of health threats
 - Coordination w/ CFSAN, ORA, OF

- Risk Analysis**
- Time sensitivity
 - Time value
 - Risk of not doing
 - Risk of alternative or negative outcomes

- Collaborations**
- Leveraging resources
 - External support
 - Support by advisors
 - Strategic plan alignment
 - Alignment w/ tactical goals

Implementation factors

- Complexity**
- How hard?
 - What resources required?

- Quality**
- Experimental design
 - Scientific merit

- Availability**
- Funding
 - Expertise
 - Staff
 - Animal
 - Facility
 - Equipment
 - Software

- Feedback**
- Evaluation
 - Score and Priority
 - Follow-up

Solicit ideas, data gaps, needs, from program offices, stakeholders, and scientists

Can we do it?





Research Metrics

OR's Annual Report - reviewed by
CMT & CVM staff

Facilities and personnel

Research accomplishments

Premarket / Drug review

Compliance

Post-approval monitoring

Animal feed safety

Leveraging

Publications/Presentations

Final reports

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES USA

Center for Veterinary Medicine
Protecting Human and Animal Health

FDA Center for Veterinary Medicine

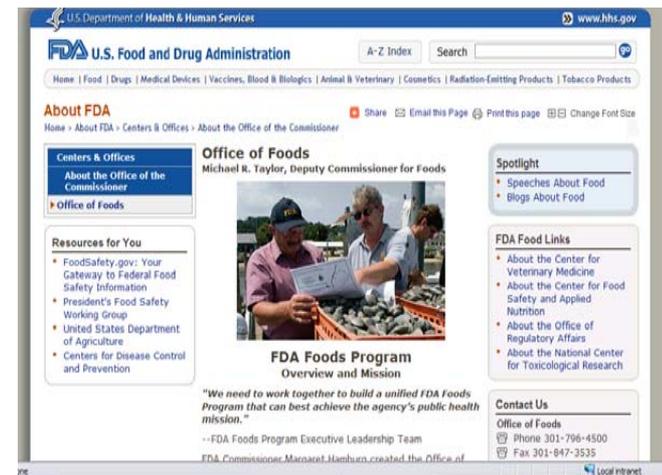
Office of Research

**ANNUAL REPORT
FY09**

The FDA/CVM Office of Research conducts applied research in support of current and evolving FDA regulatory issues. We provide research solutions that ensure the safety of animal derived food and animal health products.

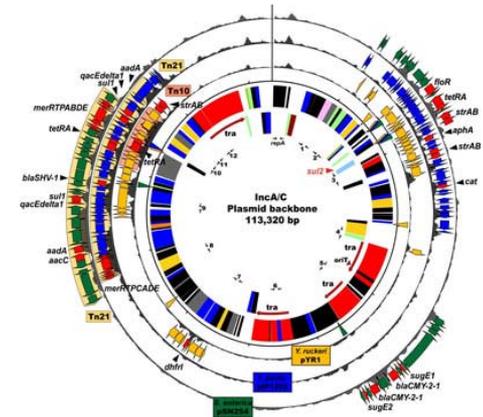
CVM Research Strategy

- Use of technologies to align research with regulatory needs
 - Strengthening our capabilities in “omics” to ensure safety of foods and drugs
- Critical Path
 - Better Evaluation Tools – Developing new biomarkers and disease models
 - Pharmacogenomics
 - Biomarkers in Animals
 - Developing products to address urgent public health needs
 - Food and feed safety
- Foods Program Research Plan
 - Coordinated development and validation of detection methods for drug residues and resistant foodborne pathogens in foods and feeds



Premarket/Drug Review

- Animal Drug Safety and Efficacy
- Antimicrobial Resistance Mechanisms
- Immunopharmacology
- Metabolism and Residue Depletion
- Method Trials
- Microbiological Methods
- Pharmacokinetics/Pharmacodynamics



A New Era of Biotechnology



- The first genetically engineered (GE) animal NADA was approved by CVM February 2009
- GE goats make Antithrombin III (Atryn®) in their milk
- OR worked with the sponsor's team to develop and validate a real-time PCR regulatory assay suitable for identifying the GE goats
- The assay provides the agency the ability to be able to identify GE goats
- Future studies will require scientist from OR working with sponsors in the pre-approval process to develop assays to detect GE animals

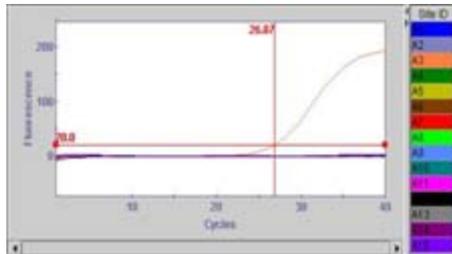
SCIENTIFIC AMERICAN

Feb 9, 2009 04:00 PM in Health | 0 comments | Post a comment

FDA approves blood-thinner Atryn made from genetically engineered goats

By Jordan Lita in 60-Second Science Blog

<http://www.sciam.com/blog/60-second-science/post.cfm?id=fda-approves-blood-thinner-atryn-ma-2009-02-09>

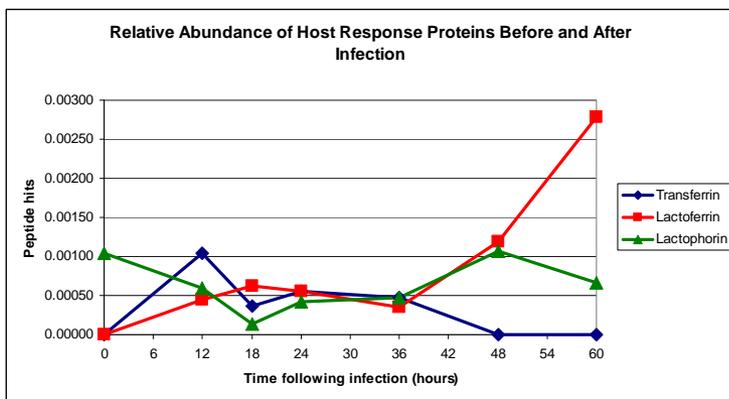


Survey of the Bovine Milk Proteome



Proteomic methods developed to evaluate changes in milk proteins during infection using:

- 2D gels and MALDI-TOF MS
- LC and tandem MS



Profiles generated on the relative abundance of:

- major milk proteins
- host response proteins
- acute phase proteins
- other inflammatory markers

Methods will be used to profile biomarkers of inflammation in the milk of dairy goats for use in evaluating the efficacy of NSAIDs in treating inflammation associated with mastitis



Compliance

~~Harmful
Residues~~

- Drug residue detection methods
- Incursion services
- Method trials and validation
- Pharmacokinetics and residue depletion
- Screening tests



Multi-class Residue Methods

- Drug residue methods
 - Develop regulatory methods for specific problems, *e.g.* chloramphenicol and nitrofurans in imported shrimp
 - Develop multiclass multiresidue screening & confirmatory methods for drugs residues in meat, eggs and fish

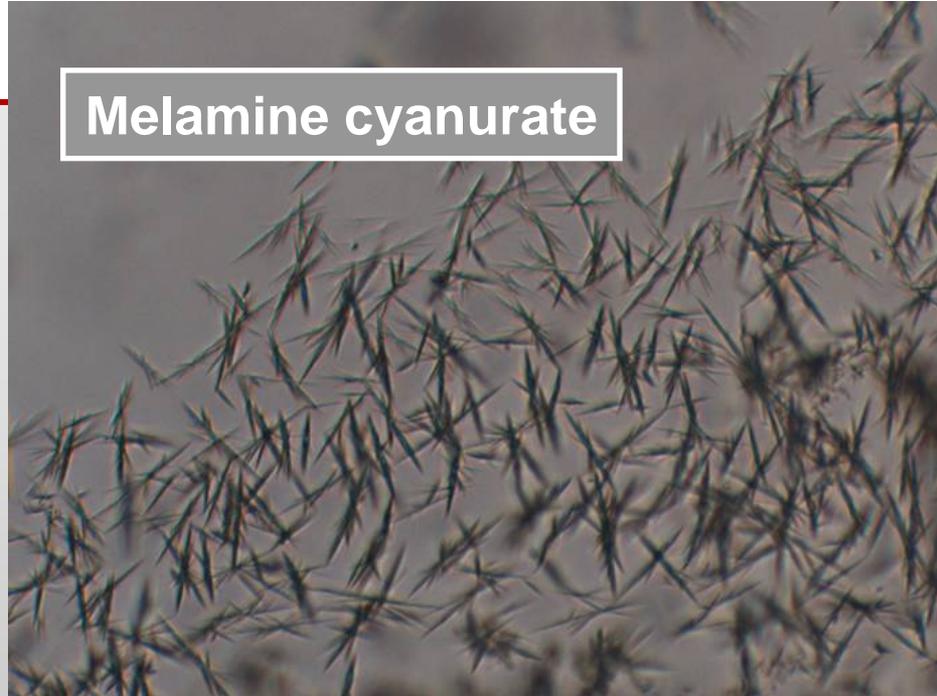
- Screen/Confirmation in Finfish
 - Single LC-MSⁿ qualitative analysis
 - Single extraction scheme
 - Total of 36 drugs
 - Four species of fish: salmon, trout, catfish, tilapia



The Keffau

Melamine Research

Melamine cyanurate



Global concern of triazine animal feed contamination

Determined depletion of melamine residues in fish, and initiated No Observable Effect Level (NOEL) tests for melamine kidney crystal formation, to facilitate FDA's risk assessment efforts

Animal Feed Safety



- Assurance of the safety of animal feed and feed commodities is one of the central regulatory obligations of CVM
 - Development and evaluation of analytical methods for detection of unsafe contaminants in feeds
 - BSE – Detecting prohibited substances
 - Chemical method development
 - Conduct of microbiological surveys of feed commodities for contamination with foodborne pathogens
 - *Salmonella* in animal feeds

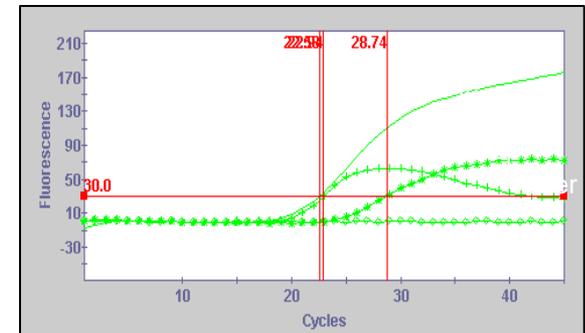


- Vet-LRN



Molecular Detection of Animal Proteins in Animal Feed

- The 1997 FDA Feed Ban prohibited adding mammalian proteins to ruminant feed
 - Cattle, sheep, goat, deer and elk main concern
- FDA currently uses feed microscopy to detect and PCR to confirm
 - Time consuming with low sample processing rate
- Have developed a **multiplex PCR method** to detect all 5 species listed above
- Represents a significant advancement sample throughput



Post-Approval Monitoring

- Surveys - Microbiological
- Microbiological Methods
- Method Trials – Microbiological



PFGE-SmaI+PFGE-KpnI
SmaI/KpnI

PFGE-SmaI PFGE-KpnI

					Date	
	CVM #	State	Source	Isolated	Species	
	N100	CA	Chicken Breast	10/04	C. jejuni	
	N105	CA	Chicken Breast	10/04	C. jejuni	
	N108	CA	Chicken Breast	10/04	C. jejuni	
	N110	CA	Chicken Breast	11/04	C. jejuni	
	N285	CT	Chicken Breast	09/04	C. jejuni	
	N288	CT	Chicken Breast	09/04	C. jejuni	
	N288	CT	Chicken Breast	09/04	C. jejuni	
	N374	MN	Chicken Breast	08/04	C. jejuni	
	N715	OR	Chicken Breast	10/04	C. jejuni	
	N720	OR	Chicken Breast	10/04	C. jejuni	
	N721	OR	Chicken Breast	10/04	C. jejuni	
	N722	OR	Chicken Breast	10/04	C. jejuni	
	N734	OR	Chicken Breast	12/04	C. jejuni	

Standardized Testing Methods

JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 2003, p. 4318-4323
0095-1137/03/\$08.00+0 DOI: 10.1128/JCM.41.9.4318-4323.2003
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Vol. 41, No. 9

Antimicrobial Susceptibility Testing of Aquatic Bacteria: Quality Control Disk Diffusion Ranges for *Escherichia coli* ATCC 25922 and *Aeromonas salmonicida* subsp. *salmonicida* ATCC 33658 at 22 and 28°C

R. A. Miller,^{1*} R. D. Walker,¹ A. Baya,² K. Clemens,³ M. Coles,⁴ J. P. Hawke,⁵ B. E. Henricson,⁶ H. M. Hsu,⁷ J. J. Mathers,⁸ J. L. Oaks,⁹ M. Papapetropoulou,¹⁰ and R. Reimschuessel¹

Vol. 64: 211-222, 2005	DISEASES OF AQUATIC ORGANISMS Dis Aquat Org	Published May 20
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Standardization of a broth microdilution susceptibility testing method to determine minimum inhibitory concentrations of aquatic bacteria

R. A. Miller^{1,*}, R. D. Walker¹, J. Carson², M. Coles³, R. Coyne⁴, I. Dalsgaard⁵, C. Gieseke¹, H. M. Hsu⁶, J. J. Mathers⁷, M. Papapetropoulou⁸, B. Petty⁹, C. Teitzel¹⁰, R. Reimschuessel¹

JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2005, p. 6136-6138
0095-1137/05/\$08.00+0 doi:10.1128/JCM.43.12.6136-6138.2005
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Vol. 43, No. 12

Broth Microdilution Susceptibility Testing of *Campylobacter jejuni* and the Determination of Quality Control Ranges for Fourteen Antimicrobial Agents

Patrick F. McDermott,^{1*} Sonya M. Bodeis-Jones,¹ Thomas R. Fritsche,² Ronald N. Jones,² Robert D. Walker,¹ and the *Campylobacter* Susceptibility Testing Group

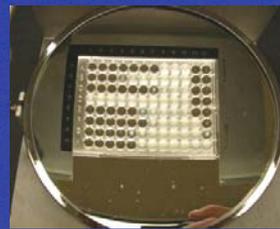
M42-A
Vol. 26 No. 23
Replaces M42-P
Vol. 25 No. 21

Methods for Antimicrobial Disk Susceptibility Testing of Bacteria Isolated From Aquatic Animals; Approved Guideline



M49-A
Vol. 26 No. 24
Replaces M49-P
Vol. 25 No. 22

Methods for Broth Dilution Susceptibility Testing of Bacteria Isolated From Aquatic Animals; Approved Guideline



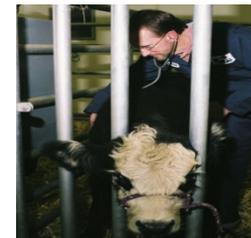
This document provides the most up-to-date techniques for the determination of minimal inhibitory concentrations (MICs) of aquatic bacteria by broth micro- and macrodilution, and criteria for quality control testing.
A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

This document provides the method for the testing of aquatic species isolated from aquatic animals.
A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

CLINICAL AND LABORATORY STANDARDS INSTITUTE
(formerly NCCLS)

National Antimicrobial Resistance Monitoring System (NARMS)

- Provide data on extent, temporal trends in enteric bacteria
- Collaboration among:
 - FDA/CVM (retail meat)
 - CDC (humans)
 - USDA (food animals)
- Platform for research
- Help FDA decision-making in approval of veterinary, human drugs
 - Promote antimicrobial stewardship
 - Supports the Agency's mission as a science-based regulatory agency



Leveraging Activities

CVM works with others outside FDA in ways that will help the Agency meet its public health responsibilities

- **CDC**
 - NARMS
 - PulseNet
 - FoodNet
- **USDA**
 - National Center for Cool and Cold Water Aquaculture
 - Bee Research Laboratory
 - Bacterial Epidemiology and Antimicrobial Resistance Research Unit
- **Academia**
 - Universities of Maryland
 - University of Minnesota, NCSU, Ohio State University, University of Georgia, Iowa State University, Howard University, NDSU, Marshfield Clinic
- **Florida Department of Agriculture**
- **AOAC International**
- **EU Community Reference Laboratories**
- **2010 - VERN**

**Look beyond the boundaries of
our laboratories
Develop new partnerships**

Research Publications

Clinical Infectious Diseases
Journal of Bacteriology
Foodborne Pathogens and Disease
Journal of Food Protection
Antimicrobial Agents and Chemotherapy
Applied and Environmental Microbiology
Journal of Clinical Microbiology
Avian Diseases
PLoS One
Veterinary Microbiology
Emerging Infectious Diseases
American Journal of Veterinary Research
Molecular and Cellular Probes

Journal of Aquatic Animal Health
Journal of Veterinary Pharmacology and Therapeutics
International Journal of Toxicology
Toxicological Sciences
Journal of Agriculture and Food Chemistry
Journal of Chromatography
Journal of AOAC International
Journal of Chromatography B
Rapid Communications in Mass Spectrometry
Pathobiology
Journal of Dairy Science

OR Publications

JOURNAL OF
AGRICULTURAL AND
FOOD CHEMISTRY

Multiclass Determination of Antibiotic Residues

MAYDA I. LOPEZ,*[†] JEFFERY S.

Center for Veterinary Medicine, U.S. Food and Drug Administration, 1090 Willow Grove Road, Laurel, Maryland 20708, and Bee Research, Inc., 10000 Beechwood Drive, Laurel, Maryland 20708

A multiclass method has been developed for the determination of tetracyclines (chlortetracycline, doxycycline, ciprofloxacin, danofloxacin, difloxacin, enrofloxacin, flumequine, and sarafloxacin), aminoglycosides (streptomycin, gentamicin, and neomycin), macrolides (lincosamides), and fumagillin residues using LC-MS/MS. Erythromycin (a macrolide) and metronidazole were not quantitated. Honey samples (~2 g) were extracted into 10 mL of the supernatant is used to determine the presence of residues. A fine-mesh nylon fabric and cleaned up the sample reconstitution, 15 antibiotics are analyzed simultaneously in positive ion mode. Afterward, chloranil was used as a matrix. This method has been validated at the low pH range between 65 and 104% and coefficients of variation were caused by honey of different floral origin.

KEYWORDS: Antibiotics; honey; multiclass

VOLUME 24 **August 2008** NUMBER 8
Laboratory Information Bulletin

- 4421** Determination of Melamine and Cyanuric Acid Residues in Infant Formula using LC-MS/MS
Sherri Turnipseed, Christine Casey, Cristina Nochetto, and David N. Heller
- 4422** Interim Method for Determination of Melamine and Cyanuric Acid Residues In Foods using LC-MS/MS: Version 1.0
Michael Smoker and Alexander J. Krynitsky
- 4423** GC-MS Screen for the Presence of Melamine, Ammeline, Ammelide, and Cyanuric Acid
Jonathan J. Litzau, Gregory E. Mercer, and Kevin J. Mulligan



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Office of Regulatory Affairs
Office of Regional Operations
Division of Field Science

Vol. 74, No. 21

Salmonella enterica Serovar Heidelberg in Poultry, from 2002 to 2006⁷

K. Blickenstaff, S. L. Ayers, J. W. Abbott, E. McDermott*

*University of Maryland System, Center for Veterinary Medicine, P.O. Box 7000, College Park, Maryland 20742

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August 2008

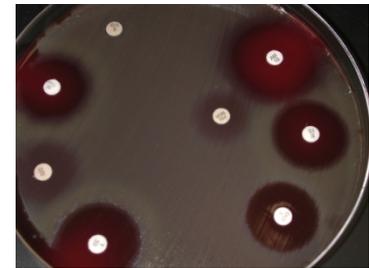
Salmonellosis is a common zoonotic illness in humans. There are few data on the prevalence of *Salmonella enterica* serovar Heidelberg in poultry. In a sampling of 20,295 meats, including ground beef ($n = 5,100$), and pork chops ($n = 5,100$), and chicken breast ($n = 10,095$), 110 (36.9%) were from chicken breast, and 109 (36.9%) were from ground beef. One hundred ninety-eight isolates (66.4%) were resistant to at least five compounds. Six isolates were resistant to all six antimicrobials. The highest resistance in poultry was to tetracycline (27.7%), gentamicin (10.4%), and cefotaxime (9.0%). All of the resistant strains carried *bla*_{CMY}. PFGE analysis of these data indicate that *Salmonella enterica* serovar Heidelberg is a widespread clone of multidrug-resistant

CVM OR Research – Summary

- Focused on two critical path areas and FPRP
 - Developing new biomarkers and disease models
 - Developing methods for drug residues and resistant foodborne pathogens in foods and feeds

- Designed to identify and develop scientifically sound solutions to new concerns that are likely to arise regarding the safety, quality, and efficacy of new and existing FDA regulated products
 - Premarket/Drug review
 - Compliance
 - Post-approval monitoring
 - Animal feed safety

- Provide the scientific basis on which to base new procedures, policies, and regulations



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Animal & Veterinary | Share | Email this Page | Print this page | Change

Home > Animal & Veterinary

Pet Food
FDA's regulation of pet food, pet food labeling, and pet food safety.

Pet Health & Safety Widget
Place this widget on your web site, portal home page, or in your blog to allow you and your visitors to get information about pet health and safety from the Center for Veterinary Medicine.

Genetically Engineered Animals
FDA's regulation of genetically engineered animals.

Development & Approval Process
New Animal Drug Applications, Electronic Submissions, User Fees, Genetic Engineering, Minor Use/Minor Species, Aquaculture, Food Additive Petitions

Guidance, Compliance & Enforcement
BSE (mad cow disease), Policies & Procedures Manual, Laws

News & Events
CVM Updates, FDA Veterinarian Newsletter, Meeting Announcements

Products
Approved Animal Drug Products, Animal Food/Feed, Imports & Exports

Resources for You
Animal Health Literacy, Consumer Information, FDA and the Veterinarian

Safety & Health
Adverse Drug Events, Product Safety, Animal Feed Safety System (AFSS), Antimicrobial Resistance, Animal Cloning, Recalls

Science & Research
Research Areas, Publications

Spotlight

- Reportable Food Regi for Industry
- Animal Cloning
- CVM Updates
- Salmonella and Turtle Safety
- Bovine Spongiform Encephalopathy

Recalls & Alerts

- Pet Food Recalls
- How to Report An Ad Drug Experience
- How to Report a Pet Complaint

Approvals & Clearance

- New Animal Drug Applications
- Animal Drugs @ FDA

CVM Information

- About the Center for Veterinary Medicine
- CVM Ombudsman
- Veterinary Medicine Student Internships
- CVM FOIA Electronic Reading Room

