CVM’s Core Responsibilities

- **Pre-market evaluation:** new animal drugs and animal feeds for safety and efficacy
- **Post-approval monitoring:** animal drugs, feeds, and marketed animal devices
- **Compliance:** ensure conformity with existing regulations
- **Research:** support regulatory decision-making

CVM’s Major Challenges

- Unapproved animal drug products
- Pet food protection & human food protection
- Issues related to new animal drug efficacy & safety
- Animal biotechnology (regulating genetic engineering and cloning)
- Addressing antimicrobial resistance (GFI-152, NARMS)
- Minor use / minor species (MUMS)
- Preventing the transmission of bovine spongiform encephalopathy (BSE) through animal feed

To conduct research to ensure public health, the safety of animal health products and the safety of animal feed
CVM’s Office of Research (OR)

• >165 acres
• About 75 staff
• Large-animal housing and surgery suites
  • Beef & dairy cattle, meat & dairy goats, sheep, pigs, poultry
• Specialized laboratories
• Aquaculture
  • Fresh & salt water
• Fifteen 2-2.5 acre pastures
• Feed mixing facility
• Quarantine facility

Large Animal Research Facilities

Milk and meat safety
Antimicrobial resistance (AV)
Aquaculture research
Cardiovascular disease research (CDRH)
Biomarker research

Office of Research - Laboratories

• Residue Chemistry
  • Dr. Phil Kijak, Director

• Applied Veterinary Research
  • Dr. Jeff Ward, Director

• Animal and Food Microbiology
  • Dr. Mark Rasmussen, Director
OR Capabilities

- Research programs
  - Food and companion animals
  - Efficacy & Safety
  - Animal and public health
- Specialized and unique facilities/instruments
- Diverse scientific backgrounds
  - Provide training
  - Assistance for drug reviews
- Leveraging / Collaborations
  - CFSAN/ORA/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.

OR Scientists’ Training

- Animal/Dairy/Food Science
- Chemistry/ Biochemistry
- Biology/Microbiology/Molecular Biology
- Epidemiology
- Immunology
- Pharmacology
- Pathology
- Toxicology
- Veterinary Medicine

Prioritizing Research

Identify research needs with pre-and post market CVM offices
- Yearly planning meetings with
  - ONADE
  - OS&C, OMUMS
  - Other Centers needs and Agency programs

Three Year Plan
- Internal Prioritization of research
- Prepared by OR
- Center Management Team (CMT) reviews & approves
Research Metrics: Annual Report

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
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

Look beyond the boundaries of our laboratories
Develop new partnerships

CVM Research Initiatives

- Critical Path
  - Better Evaluation Tools - Developing new biomarkers and disease models
    - Pharmacogenomics
    - Biomarkers in Animals
    - Drug safety & drug efficacy
  - Developing products to address urgent public health needs
    - Food and feed safety
- Foods Program Research Plan
- Use technologies to align research with regulatory needs
  - Strengthening our capabilities in “omics” to ensure safety of foods and drugs

FDA Science Board Subcommittee
Review of CVM’s Research Program

The FDA Science Board Advisory Committee established a subcommittee to evaluate CVM’s Research Program (2009)

- Visited OR Campus on July 15-16, 2009
- Subcommittee was deeply impressed by the dedication to mission and quality science
- The research campus is modern and well-maintained, providing a pleasant atmosphere for researchers and staff
- OR researchers strive to (and frequently succeed in) publishing research results in top tier journals in relevant disciplines
- The knowledge and excellence of OR scientists are recognized by their peers outside of the CVM
Science Board Recommendations

- Build capacity to advance & lead regulatory science
- Develop a communications strategy to more effectively disseminate findings
- Enhance opportunities for OR scientists to interact with experts in academia, other government organizations, & industry
- Seek engagement with leading scientists from academia and industry
- Solicit advice from a Board of External Scientific Counselors (from FDA Science Board)

Division of Residue Chemistry
Program Areas

- Develop analytical methods to detect veterinary drugs and feed contaminants
  - Replacement of old residue methods
  - Detection of feed contaminants
  - Develop methods to support PK studies
- Validate methods submitted in support of NADAs
- Methods for veterinary drugs in food
- Milk test kit program

Division of Applied Veterinary Research
Program Areas

- Aquaculture Research
- Genomics/Proteomics
- Pharmacokinetics/Pharmacodynamics
- Support Services

In support of:
- FDA Foods Program
- Pre-Market drug approval
- Minor Use/Minor Species
- Critical Path Initiative
Division of Animal & Food Microbiology

Program Areas

- Standardize and validate in vitro antimicrobial susceptibility testing methods
- Measure the effects of veterinary antimicrobials on emergence of resistance in zoonotic foodborne bacteria
- Determine the genetic diversity within bacterial populations
  - Genetic relationships between isolates from different sources
  - Plasmid epidemiology/biology
- Characterize molecular mechanisms of resistance
  - Develop rapid methods to identify/characterize resistant bacteria
- Examine the role of animal feeds (rendered products, dried commodities, complete feeds) in the ecology of resistance
- NARMS

Organization of OR Studies

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

Post-Approval Monitoring:

Animal Feed Safety:

Compliance:
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

Genomics/Proteomics Research

Agency/Center Aims
- Individualized medicine
- Adverse drug responses
- Data standards/evaluation
- Bioinformatics
  - Identification and Verification of Inflammatory Biomarkers & Inflammation Models in Swine
    - Demonstration of NSAID efficacy
    - Genomics approach
  - Identification of Inflammation Biomarkers and Models in Ruminants (Dairy goats & dairy cattle)
    - Demonstration of NSAID efficacy
    - Proteomics approach

Survey of the Bovine Milk Proteome

Proteomic methods developed to evaluate changes in milk proteins during infection/inflammation using:
- 2D gels and MALDI-TOF MS
- LC and tandem MS
Goal: Identification of biomarkers to support anti-inflammatory claims of NSAIDs

Profiles generated on the relative abundance of:
- major milk proteins
- host response proteins
- acute phase proteins
- other inflammatory markers
Pharmacogenomics of the MDR-1 Gene Mutation and the Effect on P-Glycoprotein Substrates in Dogs

- A multi-year study to explore the impact of multidrug resistance-I (MDR-1) gene mutation on drug safety in dogs
  - To determine whether systemic drug exposure of known P-gp substrates differ when administered to dogs that are homozygous recessive, heterozygous or wild-types
    - Renally cleared
    - Hepatic/biliary cleared
    - Issues pertaining to stereospecificity
  - Develop in vivo and in vitro models to determine whether a P-gp substrate poses issues of target animal safety

Minor Use/Minor Species (MUMS)

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<tr>
<th>Anthelmintic</th>
<th>Approval</th>
<th>Mode of Administration</th>
<th>Last Sample</th>
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<tbody>
<tr>
<td>Moxidectin</td>
<td>LIV</td>
<td>Oral</td>
<td>2 (c, s, g)</td>
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<tr>
<td>Ivermectin</td>
<td>IVR</td>
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<td>Doramectin</td>
<td>DOR</td>
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<tr>
<td>Pyrantel</td>
<td>PRT</td>
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</table>

Time (days) Administration Species Brand Name Abbreviation Anthelmintic Last Sample Means of Approval

Compliance

- Drug residue detection methods
- Incursion services
- Method trials and validation
- Pharmacokinetics and residue depletion
- Screening tests
Replacement of Obsolete Official Methods

- Old official methods
  - Outdated scientifically
  - Labor intensive
  - Safety
    - Scientist
    - Environment
  - Equipment
- Tolerance is based on Official Method
- Need to bridge new method to older one

Penicillin G in Bovine Tissue

- Developed new LC-MS/MS based method
  - Designed to be multiresidue
  - Currently being bridged to official assay
- Collaborating with FSIS

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-MS qualitative analysis
  - Single extraction scheme
  - Total of 36 drugs
  - Four species of fish: salmon, trout, catfish, tilapia
Antiviral Drugs in Poultry

- Use prohibited in turkey, chicken, duck
- Agency needed monitoring method
- Developed method for four antivirals in chicken and eggs

DNA Barcoding

- Method development at OR/DAR for FDA field labs
- PCR-based analysis of Cytochrome C Oxidase Subunit I
- Identification of >70 species
- RFE barcode reference library
- Health impact; economic fraud

Melamine Research

- 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

Molecular Detection of Animal Proteins in Animal Feed

• The 1997 FDA Feed Ban prohibited adding mammalian proteins to ruminant feed
  • Cattle, sheep, goat, most concern
  • deer and elk minor concern
• FDA previously used feed microscopy to detect and PCR to confirm
  • Time consuming with low sample processing rate
• Have developed a Real-time PCR-based method to detect three species of concern
• Represents a significant advancement sample throughput

Post-Approval Monitoring

• Surveys - Microbiological
• Microbiological Methods
• Method Trials – Microbiological
Standardized Testing Methods

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

NARMS Objectives

1. Monitor trends in antimicrobial resistance among foodborne bacteria from humans, retail meats, and animals
2. Disseminate timely information on antimicrobial resistance to promote interventions that reduce resistance among foodborne bacteria
3. Conduct research to better understand the emergence, persistence, and spread of antimicrobial resistance
4. Assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals
CVM OR Research – Summary

- Focused on two critical path areas and FPP
  - 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

Welcome!