MINUTES
MINOR USE ANIMAL DRUG PROGRAM/NRSP-7 FALL MEETING 2010
OCTOBER 4TH AND 5TH, 2010

The USDA's Minor Species Animal Drug Program, National Research Support Project #7 (NRSP-7) held its semi-annual meeting of the technical committee and administrative advisors on October 4h and 5th, visiting MacFarlane Pheasants, Inc, Janesville, WI and Pfizer Animal Health, Kalamazoo, MI.

MONDAY OCTOBER 4TH, 2010

LOCATION: MacFarlane Pheasants, Inc. 2821 South U.S. Hwy 51, Janesville, WI USA 53546

ATTENDANCE AT FARM MEETING

NAME	AFFILIATION	EMAIL ADDRESS
Dorothy Bailey	FDA/CVM	dorothy.bailey@fda.hhs.gov.
John C. Baker	AA/MI AES	Baker@anr.msu.edu
John G. Babish	NRSP-7	jgb7@cornell.edu
Bill MacFarlane	MacFarlane Pheasants	bill@pheasant.com
Lisa Tell	NRSP-7/UC Davis	latell@ucdavis.edu
Meg Oeller	FDA/CVM	moeller@cvm.fda.gov
Ron Griffith	NRSP-7/Iowa State	rgriffit@iastate.edu
Bret W. Hess	University of Wyoming	BretHess@uwyo.edu
Thomas Vickroy	NRSP-7/U FL	vickroy@vetmed.ufl.edu

8:30 – 11:30 TOUR OF MACFARLANE PHEASANTS, INC.

A Tour of MacFarlane Pheasants, Inc was conducted by President Bill MacFarlane. During the tour of the facilities, the group discussed current husbandry practices and drug needs of the pheasant and game bird industry.

Following lunch with Bill MacFarlane, the group traveled to Kellogg Biological Station at Michigan State University.

7:00 to 9:30 MUADP/NRSP-7 WORKING SESSION

LOCATION: Carriage House (meeting room), Kellogg Biological Station, 3700 East Gull Lake Drive Hickory Corners, MI 49060

ATTENDEES:

NAME	AFFILIATION	EMAIL ADDRESS
Dorothy Bailey	FDA/CVM	dorothy.bailey@fda.hhs.gov.
John C. Baker	AA/MI AES	Baker@anr.msu.edu
John G. Babish	NRSP-7	jgb7@cornell.edu
Lisa Tell	NRSP-7/UC Davis	latell@ucdavis.edu
Meg Oeller	FDA/CVM	moeller@cvm.fda.gov
Ron Griffith	NRSP-7/Iowa State	rgriffit@iastate.edu
Bret W. Hess	University of Wyoming	BretHess@uwyo.edu
Thomas Vickroy	NRSP-7/U FL	vickroy@ufl.edu

Dr. John G. Babish called the meeting to order and introduced Dr. Bret W. Hess as the newly appointed Administrative Advisor for the Western Region.

ADMINISTRATIVE REPORTS

REPORT FROM THE ADMINISTRATIVE ADVISORS - Dr. John Baker (Chair)

In his report, Dr. Baker described the historical background of the Kellogg Biological Station. Dr Baker then led a short discussion on the lobbying efforts at MSU and other universities.

REPORTS FROM LIAISONS

NIFA/USDA – Dr. Gary Sherman
In his absence, Dr. Sherman provided the following written statements read by Dr. Babish:

1) The Federal Government is operating under Continuing Resolution to continue programs. This allows government operations to continue under the assumption that programs will receive the same funding as the previous fiscal year.

2) Discussions are underway at NIFA, through me, about MUADP becoming competitive using a model similar to that used by IR4. Our Policy staff point out that until a Federal budget is signed into law, and legislative language potentially associated with MUADP White House, House and Senate markup, Conference and Appropriations phases is available for review, they will not/cannot make a recommendation/determination about MUADP. For example, if Congress were to explicitly earmark MUADP to the four current universities, this would preclude NIFA from pursuing implementation of a competitive model. On the other hand, if Congress is silent on this matter, there is more flexibility. Essentially, NIFA Policy staff is not willing to assume that Congress will state no such explicit comments or preferences regarding state-specific involvement. That said, our research has shown that Congress has, in the past, not offered proscriptive language about MUADP recipient institutions. As soon as a budget bill is enacted we'll be able to push forward.

3) Level funding for MUADP is still expected but no promises until Federal budget bill is finally passed

Report from CVM – Dr. Meg Oeller
Dr. Oeller began her presentation with a handout of a review of all ADR and their current status (See Appendix I to this report). She requested that each regional coordinator review the modified listing and comment on the appropriateness of those projects listed as TERMINATED.

REGIONAL REPORTS SUBMITTED ELECTRONICALLY
Western – Dr. Lisa Tell

Progress of Work and Principal Accomplishments:
Active Regional Projects:
ADR#325 – Florfenicol (Nuflor® Injectable Solution) for sheep for respiratory disease

The human food safety (HFS) and efficacy studies required by FDA/CVM for the old formulation of florfenicol (Nuflor Injectable Solution) have been completed. All of the data from this project have been published. The data from the HFS study has been organized and a technical report written. The final technical report for the human food safety study was reviewed for Quality Assurance in March, 2010. This report was submitted to FDA/CVM in July, 2010 and is currently undergoing review.

ADR#350 – Florfenicol (Nuflor Gold®) for sheep for respiratory disease

A pilot study evaluating administration route (IM vs. SC) and doses of 20 (IM) or 40 (SC) mg/kg was performed in September and October of 2009. All of the samples (n=672; 28 samples for 24 animals) have been analyzed. A product development meeting was held on November 18th, 2009 with CVM, the sponsor and the Minor Use

Animal Drug Program. Another dose range finding study using the SC route of administration is to be performed. Once the proposed label dose is determined, the Target Animal Safety Study will be performed. Since the last meeting a subset of samples have been analyzed evaluating differences between serum and plasma samples.

ADR#299 - Pirlimycin for Dairy Goats

Project on hold until funding is identified and CIDR goat studies are completed.

ADR#295 - Strontium Chloride for Salmonids. Steve Schroeder

There is nothing to report. All information relative to this project was sent to Dr. Bowser (Northeastern NRSP-7 Region) in June 2010. CVM is going to help coordinate his oversight of this project.

ADR#338 – Spectramast™ LC Sterile Suspension for Mastitis in Dairy Goats

Project on hold until funding is identified and CIDR goat studies are completed.

ADR#135 – Erythromycin in Salmonids

The environmental assessment was sent to FDA/CVM for review and they requested a revision of certain sections and that a chronic toxicity study with *Daphnia magna* is performed. This chronic toxicity study has been performed and will address CVM concerns regarding chronic toxicity to aquatic insects. In addition, a study describing the physiochemical properties of erythromycin has been performed. Because of the physical characteristics of ERTT, an empirical pKa could not be established. The final environmental assessment report for erythromycin in salmonids was completed in May, 2010 and submitted to FDA/CVM for review. The results of this environmental assessment report supports the safe use of erythromycin thiocyanate in all freshwater-reared salmonids at a dose regimen of 100 mg/kg bodyweight/day for 21 to 28 days. Christine Moffitt, (author) has submitted the White Paper for erythromycin. This is currently under revision.

ADR# 311 – Lincomycin soluble powder for foulbrood disease in Honeybees

The human food safety technical section is complete. The effectiveness technical section is complete.

<u>Collaborative Projects:</u>

ADR# 258 - CIDRg (Controlled Internal Drug Release Devices) in Sheep

FDA/CVM has accepted all of the data for this study and the information has been summarized by FDA/CVM in a Public Master File. Completed sections are effectiveness, target animal safety, human food safety, and environmental safety. This project was announced in the Federal Register, Vol 74(220), pg 59073, November 17, 2009.

ADR#272 - Romet for Game birds

No Western region activity on this project. Need to check what region this project was originally assigned to.

ADR#280 - Fenbendazole in Game Birds (Pheasants, bobwhite quail, partridge)

A conference call with Merck/Intervet/SP was held on Thursday, February 25th. See Southern Region Report. A product development meeting was held with CVM on September 9th, 2010. Plans are in place to conduct HFS and TAS summer of 2011. Western region to perform the analytical testing of samples.

ADR#324 - Progesterone CIDRs for Goats (TAS, Milk Residue Study, and Efficacy)

The target animal safety study technical report has been accepted by FDA/CVM (February 2008). The milk residue study has been completed and the quality assurance inspection has been completed. The final technical report was sent to FDA/CVM in December 2008 and accepted October 2009. FDA/CVM has provided comments regarding the efficacy protocol. The protocol has been accepted for concurrence. The efficacy study was started at UC Davis and Iowa State University during the Fall of 2009. A quality assurance inspection was performed for the stability of progesterone in goat tissue during frozen storage in September 2009. A quality assurance inspection was performed in October 2009 for CIDR-G insertion and removal. All of the raw data from UC Davis portion of this project was submitted to the Study Sponsor, Dr. Ron Griffith in August, 2010.

ADR#340 - Tulathromycin in Goats (Collaborative project with the North Central region)

The quality assurance was performed for the target animal safety study in February and March 2008. A tissue liquid chromatography/mass spectrometry method for analysis of the samples has been validated using 664 spiked samples to validate 4 tissues. Validation of analytical methods for liver, muscle, kidney and fat samples is complete. Plasma (444) and tissue (180) samples from the target animal safety have been analyzed. The quality assurance for the target animal safety report was completed November 2009. Plasma samples from the Human Food Safety Study have been analyzed and the PK data has been generated. Tissue samples from the Human Food Safety Study (205) have been analyzed. The method validation report has been submitted to the Central Region for quality assurance review.

Other Projects/Activities:

Excede in Goats: Study has been completed in non-lactating and lactating goats. The serum and milk samples have been analyzed and the pharmacokinetic data modeled. The manuscript has been written and submitted to the Journal of Veterinary Pharmacology and Therapeutics for publication.

New Projects:

Ceftiofur for Treating *Arcanobacterium pyogenes* Respiratory Infections in Deer: 27 isolates from deer have been collected. Due to the sensitivities, and pathology associated with this organism, this project is not currently being pursued for a label claim for either tulathromycin or ceftiofur. Sensitivity results are currently being compiled for publication.

CIDRs for Deer: Historical conference calls with Dr. Albert Ramudo. At this time Pfizer has indicated that they are not interested in pursuing a label claim for deer. Need to follow up at a later date.

Laboratory Report:

Most of the activity continues as sample analysis in the laboratory. Results and plans are reported under separate projects above.

Usefulness of the Findings:

The findings from all of the studies above will be utilized to fulfill the data requirements for the FDA/CVM approval of these drugs for use in minor species.

Work Planned for Remainder of the Year:

Over the next year our primary goals are to work on helping to get the fenbendazole game bird project up and going. We will work on getting the analytical method up and

running and analyzing the samples. In addition, we will work on publishing the MIC data from the deer work and the PK data from the florfenicol in sheep work.

Manuscripts Submitted, Accepted or Published Since the Last Meeting:

Clothier, K, Leavens, T, Griffith, R, Wetzlich, S, Baynes, R, Riviere, JE, Tell, L. Pharmacokinetics of tulathromycin after single and multiple subcutaneous injections in domestic goats (*Capra aegagrus hircus).*
Submitted: Journal of Veterinary Pharmacology and Therapeutics.

Clothier, K, Leavens, T, Griffith, R, Wetzlich, S, Baynes, R, Riviere, JE, Tell, L. Tulathromycin assay validation and tissue residues after single and multiple subcutaneous injections in domestic goats (*Capra aegagrus hircus*). Submitted: Journal of Veterinary Pharmacology and Therapeutics.

Leavens, T, Tell, L, Clothier, K, Griffith, R, Baynes, R, Riviere JE. Development of PBPK model to predict tulathromycin distribution in goats. Submitted: Journal of Veterinary Pharmacology and Therapeutics.

Rowe, J, Tell, L, Griffith, R, Lee, K, Hallford, D. Progesterone Milk Residues in Goats Treated with CIDR-G® Inserts. In Press: Journal of Veterinary Pharmacology and Therapeutics.

Dore, E, Angelos, J, Rowe, J, Wetzlich, S, and Tell, L. Pharmacokinetics of ceftiofur crystalline free acid and metabolites after single subcutaneous administration in lactating and non-lactating domestic goats (*Capra aegagrus hircus*). In Press: Journal of Veterinary Pharmacology and Therapeutics.

Critical Review:

1. *Work accomplished under the original project*

The original objectives of the project were to conduct a national program to obtain minor and specialty animal drug clearances (tolerances, exemptions and registrations) in cooperation with state, federal and industry personnel to include:

a. Determination and prioritization of minor-use needs and data requirements.
b. Review, analysis and evaluation of minor-use research proposals.
c. Development and assembly of data for minor-use registrations.
d. Preparation and submission of petitions for drug registrations.

Considering these objectives, considerable progress has been made towards achieving them for each of the active projects listed above, particularly in the development of the data (the actual research), its analysis, assembly and interpretation, and submission to the FDA/CVM for review.

2. *The degree to which objectives have been met*

The degree to which these objectives have been met varies from project to project, however, in most all cases there has been progress. Those projects on which there has been no movement are reevaluated during each meeting of the NRSP-7 Technical Committee and decisions made on whether to continue to pursue them or move them into the inactive project list.

3. *Incomplete work or areas needing further investigation*

All of the projects listed above have some work that needs to be completed before they are approved by the FDA/CVM. In some cases this is just the FDA/CVM review, while in others there is work needed by the NRSP-7 project. The NRSP-7 work, which is undertaken each year within the Western Region is based on the availability of qualified and interested investigators, the capacity of the regional laboratory to validate

methods and analyze samples, and cooperation of the pharmaceutical manufacturers whose products are investigated.

SUPPLEMENT TO WESTERN REGION FALL 2010 REPORT
QUALITY ASSURANCE ACTIVITIES MARCH 2010-OCTOBER 2010

Quality Assurance Review
Final Technical Report: Tissue Residue Depletion After Multiple Subcutaneous Administration of Nuflor® (Florfenicol) Injectable Solution at a Dose of 40 mg/kg to Sheep
Human Food Safety study
University of California Davis

March 2010. Review completed and submitted to Study Director, Dr. Mike Lane.
May 2010. Responses submitted and reviewed by QA.

Quality Assurance Review
Final Technical Report: Target Animal Safety of Tulathromycin (Draxxin®) Injectable Solution in Goats
Iowa State University

November 2009. Completed QA report and submitted to Study Director, Dr. Ron Griffith.
February 2010. Responses submitted and reviewed by QA.

Quality Assurance Inspection
CIDR-G® in Goats
Efficacy Study
University of California, Davis

October 8 and 26, 2009. CIDR Insertion; CIDR Removal. Completed QA reports and submitted to Study Director, Dr. Joan Rowe.
August 2010. Responses submitted and reviewed by QA.

Quality Assurance Inspection
Stability of Progesterone in Goat Adipose and Skeletal Muscle Tissue During Frozen Storage
Human Food Safety Study
New Mexico State University

September 17-18, 2009. Animal slaughter; necropsy; tissue processing (liver, muscle, reprotract, fat); extraction of progesterone; RIA analyses in fat.
Completed QA report and submitted to Study Director, Dr. Dennis Hallford.
October 2009. Responses submitted and reviewed by QA.

Quality Assurance Inspection
Lasalocid in Ring-Necked Pheasants
Target Animal Safety Study
Iowa State University

July 27-28, 2009. Dosing/feeding; bleeding; euthanasia; necropsy. Completed in life report and submitted to Study Director, Dr. Ron Griffith.

Quality Assurance Review
Final Technical Report: Efficacy of Lasalocid in Ring-necked Pheasants
Iowa State University

March 2009. Completed QA report and submitted to Study Director, Dr. Ron Griffith.

Quality Assurance Review
Final Technical Report: Progesterone Milk Residues in Goats Treated with CIDR-G® Inserts
University of California, Davis

October 2008. Completed QA report and submitted to Study Director, Dr. Joan Rowe.

Projected Reports for QA
Lasalocid in Game Birds: TAS Technical Report to be submitted by the North Central Region.

Ivermectin in Rabbits for Treating Ear Mites: Human Food Safety technical report to be submitted from the Southern region.

Northeast Region: Dr. Paul Bowser
Progress of the Work and Principal Accomplishments
Species Grouping Project:
INAD 10-320 Oxytetracycline in Fish
INAD 10-823 Romet-30 in Fish
INAD 11-145 Florfenicol in Fish

Efforts on this project consisted of providing administrative support and oversight to the New York State Department of Environmental Conservation in their conduct of field trials under our INAD 10-320 for the use of Oxytetracycline in fish.

Ovadine (Western Chemical) Disinfection of Fish Eggs:

We have been an evaluation of the efficacy of Ovadine (Provodine Iodine, Western Chemical) as an egg disinfection compound for fish eggs with a particular emphasis on the reduction of Viral Hemorrhagic Septicemia Genotype IVb from walleye eggs. Our trial will build on preliminary efforts, funded by New York Sea Grant Program, in which we found that the consensus treatment protocol of the Great Lakes Fishery Commission (50 mg/L iodine for 30 minutes) was not completely effective in the elimination of VHSV IVb. A disinfection trial was conducted during the 2010 walleye spawning season with the collaboration of the New York State Department of Environmental Conservation. Treatments included iodine doses of 0, 50 and 100 mg/L for 30 minutes. One publication on this work has been accepted for publication and a second publication is in development.

Usefulness of the findings:

In all cases, the findings to date over the course of these projects serve as the foundation for continued work on these compounds. The Human Food Safety Studies completed to date in fish to date within the Species Grouping effort are consistent with what was expected; namely that the elimination of therapeutic compounds from the edible portion of the fish tested are within the withdrawal times currently specified for labels, or available in the literature for oxytetracycline, Romet-30 and Aquaflor (Florfenicol). The unexpected finding that tannic acid can inactivate iodophores has found immediate use in the aquaculture community. Tannic acid is commonly used to remove the adherent quality of eggs, preventing them from aggregating when they are handled in a fish hatchery. Our work highlighted the need to perform copious washes of the eggs to remove residual tannic acid before an iodophore (Ovadine) is used to reduce pathogens that may contaminate the external surface of the eggs.

Work planned for next year:
Species Grouping Project:
INAD 10-320 Oxytetracycline in Fish
INAD 10-823 Romet-30 in Fish
INAD 11-145 Aquaflor (Florfenicol) in Fish

We anticipate our efforts on this project to center around the continued provision of administrative support and oversight of Efficacy Studies of oxytetracycline in a collaborative effort with the New York State Department of Environmental Conservation. The particular focus of the efficacy trials will be for the treatment of bacterial diseases not currently on the label for treatment of bacterial diseases of cool water species such as walleyes, muskellunge and tiger muskellunge (hybrid muskellunge X northern pike). These studies will be initiated when diagnosed field cases can be identified that will lend themselves to the implementation of controlled field studies.

Ovadine (Western Chemical) Disinfection of Fish Eggs:

Data from the Ovadine work is being summarized for publication. We are also investigating the potential of indexing Ovadine.

Publications issued or manuscripts approved during the year: (**see "Principal Publications" at end of report)**

CRITICAL REVIEW (Northeast Region)
1) Work accomplished under the original project:
The original objectives of the project were to conduct a national program to obtain minor and specialty animal-drug clearances (tolerances, exemptions and registrations) in cooperation with state, federal and industry personnel. The mission of NRSP-7 is:

1. To identify animal drug needs for minor species and minor uses in major species.
2. To generate and disseminate data for safe and effective therapeutic applications, and
3. To facilitate FDA/CVM approvals for drugs identified as a priority for a minor species or minor use.

Under the framework of this mission, progress has been made in the following areas:

1. Use of hydrogen peroxide for the control of bacterial gill disease in fish.
2. Species Grouping in Fish, using the compounds Oxytetracycline, Romet-30/Romet-TC and Aquaflor as test articles.
3. Use of Ovadine for the reduction of Viral Hemorrhagic Septicemia Virus on fish eggs.

2) The degree to which the objectives have been met:

Work has focused on a number of important therapeutic compounds in aquatic animals. The work is being conducted in a deliberate manner with the goal of developing appropriate data that will be submitted in support of a label for these compounds. An initial step in this process is the publication of the data in the peer reviewed scientific literature. While we consider it extremely important to have such peer-reviewed information available for the veterinary community, should they consider an extra-label use, the ultimate goal is to secure a label for the product. As an additional goal, the work is being done in a manner that could justify a species grouping concept for finfish cultured in the United States.

3) Incomplete work or areas needing further investigation:

The development of a crop (species) grouping concept is seen as imperative for supporting efforts to gain labels for therapeutic compounds for fish. Our work on Oxytetracycline, Romet-30/Romet-TC and Aquaflor (Florfenicol) in fish is proposed to be

part of an effort to utilize those compounds as models in this effort. We expect that our efforts in developing a species grouping concept for fish will be a major undertaking in the upcoming years.

Principal Publications (during the past year):
Emily R. Cornwell, Geoffrey H. Groocock, Rodman G., Getchell, and Paul R. Bowser. 2010. Residual tannic acid destroys virucidal properties of iodine. North American Journal of Aquaculture (In Press)

North Central – Dr. Ronald W. Griffith
Progress of the Work and Principal Accomplishments
Goat CIDR-G Tissue Residue

Study report has been submitted. Mean tissue levels of progesterone 12 hours after CIDR removal were significantly lower than tissue levels in control does without CIDRs.

Goat CIDR-G Effectiveness

This study is in full swing. We have received excellent cooperation from producers in a number of states. We currently have over 600 dairy goats enrolled in the study in Iowa, California, Missouri, Minnesota and Wisconsin. On the meat goat side, we are trying to find more meat goats in the Southern U.S. to hopefully complete the studies in 2010-2011. We currently have 309 does enrolled in Iowa and Texas, which is approximately 90 short of our goal. If we do not find sufficient meat goats, we may submit the dairy goat study report separately.

Lasalocid in Pheasants Efficacy

The study was completed in 2007 and the study report submitted this summer. Keeping fingers crossed.

Lasalocid in Pheasants TAS

A second high-dose group study was completed in July. The study report is currently being prepared.

Draxxin Target Animal Safety in Goats

The study report has been submitted to the FDA/CVM. Dr. Kris Clothier has a manuscript accepted by the Journal of Pharmacology and Therapeutics.

Draxxin Tissue Residue in Goats

Study report in final stages of preparation

Draxxin Efficacy in Goats

PK/PD studies and MIC and killing kinetics data have been obtained. A partial study report on efficacy is being prepared. A manuscript is being prepared.

Bioclip in Sheep

No report. Too many projects at the moment to devote any time to this.

Southern – Dr. Thomas Vickroy
Progress of the Work and Principal Accomplishments
1. **Fenbendazole in Game Birds** (pheasants, bobwhite quail, partridge). A Product Development meeting was held via teleconference on 9 September 2010 with representatives from CVM ONADE, CVM OMUMS, industry (Brent Herrig, Intervet SP) and coordinators from the Southern, North-Central and Western regions of NRSP-7. Southern region is in process of preparing and submitting protocols for studies on human food safety (HFS) and target animal safety (TAS). Plans are in place to conduct

both the HFS and TAS studies in Summer of 2011 with the Western region to perform the analytical testing of samples.

2. **Lasalocid in Game Birds** (pheasants). This project is being carried out once again in light of problems with the initial study. The Southern Region is tasked with development and validation of an analytical method for testing of samples. This work is currently underway, although there has been a slow down as the former Chemist retired and a new one is brought on board.

3. **Ivermectin in Rabbits.** The Method Validation Report was completed and submitted to the Western Region for QA review. However, that review was put on hold owing to two factors: 1) age of the study and 2) unwillingness of the manufacturer to seek designation. The project is currently in limbo.

Overview of Other Programmatic Efforts

The Southern Region is responsible for maintaining and updating the NRSP-7 website, including MUMsRx and the RUSTi system for tracking the status of regional projects. Some of these have not been updated for quite some time and are currently undergoing a substantial overhaul. In addition, the Southern Region coordinator organizes, sets the agenda and coordinates monthly teleconferences among the regional coordinators and administrators.

Anticipated Use of Project Outcomes

The findings from all of the studies above will be utilized to fulfill the data requirements for the FDA/CVM approval of these drugs for use in minor species.

Work Planned for Remainder of the Year

Over the next quarter our primary goals are to submit the HFS and TAS protocols for fenbendazole in game birds and to gain final approval of the modified analytical method for lasalocid in pheasants. The target animal safety studies for that project are slated to begin in late spring or early summer of 2011 at the North-Central region. The Southern region will be responsible for analysis of tissue samples from that study.

ACTION ITEMS FOR FOLLOW-UP

Fenbendazole in Pheasants

Product development meeting scheduled.

1. Tom and Lisa to look at TAS data and make sure that there were not any problems with the pheasants.
2. Tom and Lisa to look at TAS protocol and see what should be asked as a exclusion for the next TAS study during product development meeting. If we need to do the TAS study (and it is not to our advantage to wait for the PD meeting, then we could try to do this part of the study this summer). We could essentially do it the same as the lasalocid TAS study. I know this is not ideal but Ron can comment on whether or not he has money he needs to spend regardless so minimizing what we do might not necessarily be necessary if it gets this part of the study done and allows us to get tissues to plan for the HFS and efficacy study the next summer. We would essentially be doing the fenbendazole study without protocol concurrence but would be modeling the study after the lasalocid TAS that had protocol concurrence. Worst case scenario is that we will have more data than less.

3. Product Development meeting: Ask for efficacy data to be admissible; touch base about partial method validation.
4. Meg/Dorothy: Get data from current INAD to support efficacy/talk with McFarlane about efficacy
5. Davis to get assay up and running during 2010. Product development meeting ask if method validation is still acceptable.
6. Ron: Get samples during summer of 2010 for Davis to work with
7. Tom: Check with Brett Herrig (brent.herrig@sp.intervet.com) about designation?? Not sure if this is already designated??
8. Tom: Target this summer for submission of protocols (HFS for sure; ?do we do TAS this summer without protocol concurrence)
9. Potential study to apply for MUMS' Grant
10. Summer 2011: Do study for HFS and efficacy?

Lasalocid in Game Birds

1. U of F: Generate questions relative to the fact that the columns can no longer be purchased for the "official method"
2. Meg: Request a conference call with CVM
3. Note: Lisa Tell and Scott Wetzlich would like to attend conference call also
4. Ron: TAS technical support will be submitted
5. Ron: What happened to samples for TAS (1x, 3x and 5x?)
6. Efficacy: Georgia investigators are writing technical report. Report has been written and QAed, but investigators need to respond to QA issues. This may be a good one for having a pre-submission conference call with CVM due to some QA issues.
7. HFS: Still waiting for assay to be worked out

Tulathromycin in Goats:

1. TAS submitted to CVM by Kris Clothier/Ron Griffith.
2. Efficacy: Lisa to do literature search regarding plasma and lung secretions correlations
3. Efficacy: Marilyn to get information to us regarding Office of Research studies
4. Efficacy: Tom to send information about diffusion method
5. Efficacy: Lisa to do PK modeling of serum data for Kris to provide new AUC's for data that was generated with rerun of diluted samples
6. Ron and Kris: Work on isolate information. MIC/AUC needs to be substantiated with kill kinetics (5 isolates)
7. HFS: Western region to get method validation written
8. HFS: Western region to finish tissue data analysis and gather data and send it to ISU
9. Lisa to follow up with Albert about designation
10. Doc 152: Dorothy or Meg to start working on

CIDRs Goats and Deer:

1. Western region to send goat data from Fall 2009 to ISU. ISU grad student who is doing HFS (meat) report will also work on compilation of efficacy data.
2. Goat HFS: To be submitted by ISU (grad student working on it currently). NOTE TO RON: Need to submit an interpretation/summary of the method validation from Dennis. Even though he gives all of the information for meat method validation, he needs to give them a summary of what was done and what it meant.

3. Both UC Davis and ISU to get ready for Fall 2010 efficacy work with goats
4. Lisa: Follow up on foreign data information for deer. Meg already has HFS data. Efficacy will need to be done in US. Need to see if we can get TAS data

Ivermectin in Rabbits:

1. Tom to check with Merial about interest in label claim (Merial product). Tom: Please check with Brett Herrig (brent.herrig@sp.intervet.com). This has priority before we proceed with anything relative to this project.
2. If there is an interest in label claim, then decide where to go from here
3. Method validation to be arriving to Davis for QA. Will send it on to ISU for QA.

Florfenicol for Sheep:

1. Western Region: QA of HFS currently underway (old formulation). Road map to be written.

New Projects:

Lisa to check with sponsor about interest for following products

1. flunixin meglumine
2. Zolvix: Meg please send Lisa a contact and forward email request.

GRD/Program Action Items:

1. Lisa to touch base with Karl/Gina to find champions for Farm Bill
2. Gary Sherman to start process to "investigate" NRSP-7 moving into competitive grant system similar to IR-4
3. Lisa to contact Joan Bowen to see interest in leading stakeholders groups
4. Tom to look into sustainable farming/family farming groups as stakeholders
5. GROUP to brainstorm for other stakeholder groups for next teleconference
6. All regional coordinators to get Appendix E filled out for NIMS system as participants

Web Site:

1. Meg to send Tom PowerPoint presentations
2. Meg to look at FAQ and give some suggestions
3. Tom is looking at overall general structure
4. Development of a protocol (non public) section
5. Development of a section where people can view current activity of a project

OTHER BUSINESS

Spring Meeting

It was tentatively decided to hold the annual spring meeting in Rockville, MD on the condition of coordinating lobbying efforts at that time. The final decision on the timing of the meeting will be made when the budget situation becomes clearer this fall after the election. This will be followed on a month-to-month basis and discussed at our monthly teleconferences.

There being no further business, the meeting was adjourned at 9:30 pm.

Tuesday October 5th, 2010 Pfizer Animal Health

The USDA's Minor Species Animal Drug Program, National Research Support Project #7 (NRSP-7) held the second day of its semi-annual fall meeting at Pfizer Animal Health, 333 Portage Street, Kalamazoo, MI 49007

MEETING ATTENDEES

NAME	AFFILIATION	EMAIL ADDRESS
Albert Ramudo	Pfizer Animal Health	albert.a.ramudo@pfizer.com
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Robert Nutsch	Pfizer Animal Health	r.nutsch@pfizer.com
Ron Griffith	NRSP-7/Iowa State University	rgriffit@iastate.edu
Steve Sutherland	Pfizer Animal Health	s.sutherland@pfizer.com
Steven Cox	Pfizer Animal Health	s.cox@pfizer.com
Susan Kotarski	Pfizer Animal Health	s.kotarski@pfizer.com
Thomas Schriemer	Pfizer Animal Health	t.schriemer@pfizer.com
Thomas Vickroy	NRSP-7/U FL	vickroy@vetmed.ufl.edu

9:15 – 9:45 Dr. John G. Babish - MUADP/NRSP-7 Background Presentation – (See Appendix II)

9:45 – 10:00 Dr. Ron Griffith - Research Summary of Draxxin (tulathromycin) approvals in sheep and goats (See Appendix III)

10:00 – 12:00 Upon completion of the presentation by Dr Griffith, discussion sessions were held concerning Draxxin Sheep and Goat Effectiveness Discussion (45 min), Draxxin Sheep and Goats Metabolism and Safety (30 min), Dr. Susan Kotarski, Draxxin Sheep and Goats Microbial Safety Discussion (cf. Appendix IV; 60 min) and Review of Protocol Templates, and eSubmitter.

There being no further business, the meeting was adjourned at 12:30 pm.

RESPECTFULLY SUBMITTED:
John G. Babish, Ph.D. Date: 9/2/10
Minor Use Animal Drug Program/NRSP-7 National Coordinator

APPENDIX I

MINOR USE ANIMAL DRUG PROGRAM (NRSP-7) ADMINISTRATIVE STATUS

NRSP-7 Administrative Status

ADR #	INAD #	PMF	Drug	Formulation	Species	Indication	NADA	Status
1	2792?	5055	Monensin	Type A	Goats	Coccidiosis	095-735	Approved
2	2876	3887	Amprolium	Type A	Pheasants	Coccidiosis	012-350	Approved
5	2875	3857	Thiabendazole	Type A	Pheasants	Gapeworm	015-875	Approved
8		5582	Albendazole	oral suspension	Goats	Liver flukes	110-048	Approved
11		3895	Ivermectin	Injection	Reindeer	Warbles	128-409	Approved
14	8544	5258	Decoquinate	Type A	Sheep	Coccidiosis	039-417	Approved
15	4254	5028	Oxytetracycline	Type A	Lobster	Gaffkemia	038-439	Approved
30	4450	5178	Bacitracin	Type A	Quail	Ulcerative enteritis	046-592	Approved
90	2792?	5014	Monensin	Type A	Quail	Coccidiosis	130-736	Approved
96		5056	Sulfa/ormetoprim	Type A	Catfish	Bacterial infections	125-933	Approved
110		5307	Ivermectin	Injection	Foxes	Ear mites	128-409	Approved
111	8170?	5012	Decoquinate	Type A	Goats	Coccidiosis	039-417	Approved
115		5020	Salinomycin	Type A	Quail	Coccidiosis	128-686	Approved
122		5042	Lasalocid	Type A	Rabbits	Coccidiosis	096-298	Approved
124		5118	Fenbendazole	Oral suspension	Goats	GI Parasites	128-620	Approved
125		5059	Ivermectin	Injection	Am Bison	Hypodermosis	128-409	Approved
127		5071	Fenbendazole	Type A	Bighorn sheep	Lungworms	121-473 131-675	Approved
137		5157	Sulfa/ormetoprim	Type A	Partridges	Coccidiosis	040-209	Approved
144	6272	5366	Morantel tartrate	Type A	Goats	GI Parasites	092-444	Approved
165	6586	5544	Ceftiofur	Injection	Sheep	Baterial pneumonia	140-338	Approved
169		3543	Formalin	Immersion	Shrimp	Ext protozoal parasites	137-687 140-831 140-989	Approved
171	9266	5671	Ceftiofur	Injection	Goats	Bacterial pneumonia	140-338	Approved
191	6865	5429	Lasalocid	Type A	Partridges	Coccidiosis	096-298	Approved
217	10-772	5783	Tylosin	WSP	Honey bees	American foulbrood	013-076	Approved
238		5228	Formalin	Immersion	Fin fish & eggs	Ext protozoal parasites	140-989	Approved
245	8096 8054 8512	5667	Oxytetracycline	Immersion	Fin fish	Skeletal marking	008-622 130-435 200-247	Approved
246	9693	5673	Tilmicosin	Injection	Sheep	Chronic resp disease	140-929	Approved
258	10-321	5947	Progesterone	CIDR	Sheep	Out-of-season breeding	141-302	Approved
17		3883	Ivermectin	Oral suspension	Goats	GI parasites		PMF
87	4449	5433	Amoxicillin	Injection	Sheep	Bacterial pneumonia		PMF
95		5117	Levamisole	Oral suspension	Goats	GI parasites		PMF
112	4543	5440	Clorsulon	Oral suspension	Goats	Liver flukes		PMF
107	9557	5421	Ivermectin	Injection	Rabbit	Ear mites		Active
135	6013	5165	Erythromycin	Type A	Salmonids	Bacterial Kidney Disease		Active
216	10-993		Fenbendazole	Type A	Fallow Deer	GI parasites		Active
235	9096		Lasalocid	Type A	Pheasants	Coccidiosis		Active
271	9757		Carp Pituitary	Injection	Fin fish	Spawning aid		Active

NRSP-7 Administrative Status

ADR #	INAD #	PMF	Drug	Formulation	Species	Indication	NADA	Status
280	10-062	5644	Fenbendazole	Type A	Pheasants	Gapeworm & Cecal worm		Active
285	10-319 10-320		Oxytetracycline	Type A	Fin fish	Vibriosis		Active
294	10-746		Lasalocid	Type A	Deer	Coccidiosis		Active
295	10-536		Strontium Chloride	Immersion	Fin fish	Skeletal Marking		Active
298	10-872		Lasalocid	Type A	Goats	Coccidiosis		Active
311	10-766		Lincomycin	WSP	Honey bees	American foulbrood		Active
313	10-823		Sulfa/ormetoprim	Type A	Fin fish	Bacterial Infections		Active
324	11-389		Progesterone	CIDR	Goats	Estrus synchronization		Active
334	11-145		Florfenicol	Type A	Fin fish	Bacterial infections		Active
335	Western		Ovaprim (GnRHa +)	Injection	Ornament fish	Spawning aid		Active
336	Western		Metomidate	Injection	Ornament fish	Anesthetic		Active
339	11-513		Tulathromycin	Injection	Sheep	Respiratory infections		Active
340	11-512		Tulathromycin	Injection	Goats	Respiratory infections		Active
18	4352 9093		Chloramine-T	Immersion	Salmonids	Bacterial Gill Disease		Transfer
43	6006	5316	Oxytetracycline	Injection	Goats	Bacterial pneumonia		Closed
83	6005	5321	Oxytetracycline	Injection	Sheep	Bacterial pneumonia		Closed
231	8826		Copper sulfate	Immersion	Catfish	External protozoa		Transfer
252	10-773		Tilmicosin phosphate	Injection	Veal calf	Respiratory infection		Terminated
259	9493		Hydrogen peroxide	Immersion	Fin fish	Bacterial Gill Disease		Closed
329	11-091		Florfenicol	Injection	Veal calf	Respiratory infection		Terminated
19	4320		Oxytetracycline	Type A	Alligators	(7 subs - data)		Inactive
66	6119		Penicillin Novobiocin	Intramammary	Goats	(milk study)		Inactive
117	10-872		Lasalocid	Type A	Goats	(2 subs - meeting)		Inactive
177	6481		Enrofloxacin		Rabbits	(4 subs - data)		Inactive
178	6976		Spectinomycin	inj/oral	Ducks	(3 subs - tissue residue)		Inactive
202	8249		Ivermectin	Injection	Llamas	(2 subs - data)		Inactive
222	8798	5484	Ivermectin	Pour-on	Am Bison	GI parasites		Inactive
236	9097		Clopidol	Type A	Pheasant	Coccidiosis (data)		Inactive
272	10-804		Sulfa/ormetoprim	Type A	Pheasant	Coccidiosis		Inactive
273	10-342		Nitarsone	Type A	Partridge	Blackhead		Inactive
274	10-333		Zoamix	Type A	Pheasant	Coccidiosis		Inactive
299	11-193		Pirlimycin	Intramammary	Goats	Mastitis		Inactive
325/6	10-958		Florfenicol	Injection	Sheep	Respiratory infections		Inactive
327/8	11-836		Florfenicol	Injection	Goats	(11 subs - data)		Inactive
333	11-271		Florfenicol	Type A	Shrimp	Necrotizing pancreatitis		Inactive
14	4499		Decoquinate	Type A	Sheep	(no data)		TERMINATE
33	4406		Amoxicillin	Injection	Goats	(no data)		TERMINATE

NRSP-7 Administrative Status

ADR #	INAD #	PMF	Drug	Formulation	Species	Indication	NADA	Status
34	4447		Amoxicillin	Injection	Goats	(no data)		TERMINATE
35	4448		Amoxicillin	Oral	Goats	(no data)		TERMINATE
42	4405		Oxytetracycline	Injection	Dairy Goats	(no data)		TERMINATE
66	4411		Penicillin Novobiocin	Intramammary	Dairy goats	(no data)		TERMINATE
106	4785		Azaperone	Injection	Wild ungulates	(1st submission only)		TERMINATE
118	4414		Tiamulin	Type A	Trout	(no data)		TERMINATE
120	6492		Oxolinic acid	Type A	Salmon	(no data)		TERMINATE
131	4890		Benzocaine	Injection	Salmonids	(no data)		TERMINATE
145/6	6766		Fluoroquinolone	Type A	Salmon	(no data)		TERMINATE
172	6613		Bacitracin Zinc	Type A	Rabbits	(1st submission only)		TERMINATE
174	6302		Erythromycin	Injection	Salmon	(1st submission only)		TERMINATE
176	6725		Amoxicillin	Injection	Dairy goats	(1st submission only)		TERMINATE
179	6566		Fluoroquinolone	Oral in water	Cockatiels	(2 subs - meeting)		TERMINATE
182/206	8499		Albendazole	feed/block	Deer	(no data)		TERMINATE
187	6818		Avermectin	Bio bullet	Deer	(1st submission only)		TERMINATE
188	6823		Avermectin	Bio bullet	Sheep	(1st submission only)		TERMINATE
190	6862		Ceftiofur	Bio bullet	Bighorn Sheep	(3 subs - ???)		TERMINATE
197	8258		Ivermectin	Pour-on	Red Deer	(no data)		TERMINATE
199	8603		Enrofloxacin	Soluble powder	Shrimp	(no data)		TERMINATE
202	8800		Clorsulon Ivermectin	Injection	Llamas	(1st submission only)		TERMINATE
209	8500		Amoxicillin	Type A	Salmon	(no data)		TERMINATE
215	8558		Sarafloxacin	Type A	HSB (fish)	(1st submission only)		TERMINATE
251	9398		Ceftiofur	Injection	Deer	(meeting only)		TERMINATE
253	9481		Fenbendazole	Type A	Bison	(1st submission only)		TERMINATE
257	9476		Oxytetracycline	Type A	Lobster	(meeting only)		TERMINATE
275	11-898		Ceftiofur CFA	Injection	Deer	(1st submission only)		TERMINATE
284	10-146		Melengestrol acetate	Oral	Sheep	(1st submission only)		TERMINATE
297	10607		Triclabendazole	Oral drench	Deer Elk	(1st submission only)		TERMINATE

APPENDIX II

MINOR USE ANIMAL DRUG PROGRAM (NRSP-7) PRESENTATION

Minor Use Animal Drug Program
NRSP-7

A NATIONAL AGRICULTURAL PROGRAM
TO APPROVE MINOR USE ANIMAL DRUGS AND
DISSEMINATE INFORMATION ON THEIR SAFE AND
EFFICACEOUS USE

A Presentation for Pfizer Animal Health

John G. Babish, Ph.D.
National Coordinator

October 5, 2010

Mission Statement

The mission of NRSP-7 is:

1. *Identify* animal drug needs for minor species and minor uses in major species,
2. *Generate* and *disseminate* data for safe and effective therapeutic applications, and
3. *Facilitate* FDA/CVM approvals for drugs identified as a priority for a minor species or minor use.

To accomplish these goals, NRSP-7 functions through the coordination of efforts among animal producers, pharmaceutical manufacturers, FDA/CVM, USDA/Cooperative State Research, Education, and Extension Service, universities, State Agricultural Experiment Stations and veterinary medical colleges though out the country.

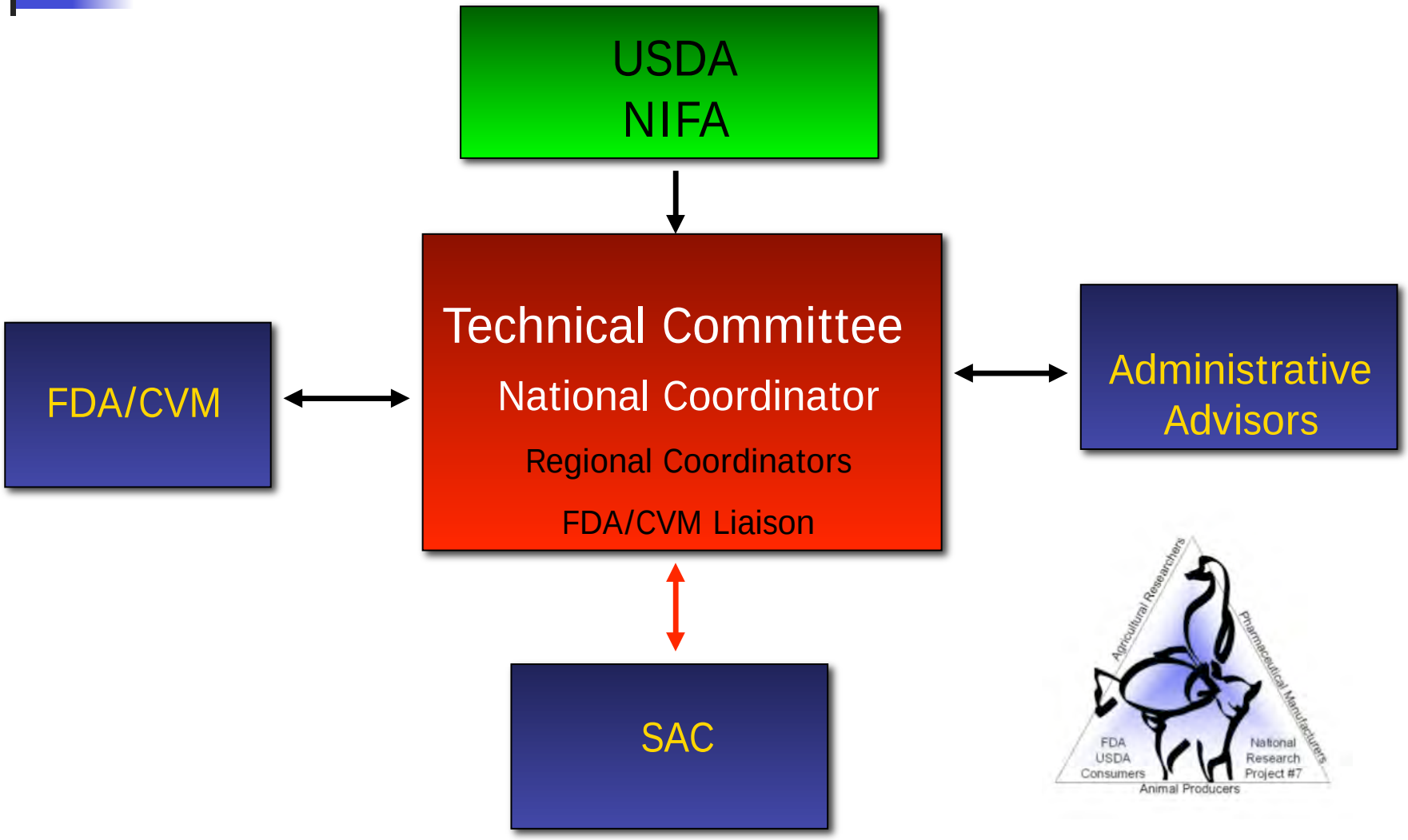
Economic Impact of Minor Animal Species in US is Great but at Risk

INDUSTRY	LEADING STATES	US FARM GATE VALUE [$M]	US ECONOMIC IMPACT [$M]
Game Bird	TX, NC, PA, KS, WI, NY, IL, SD, FL, MN, IA, GA, MS, IN & AL.	$830	$5,000
Rabbits	CA, GA, OH, PA, & TX	$20	$831
Honey Bees	ND, CA, SD, FL, MT, MN, TX, & WI.	$153	$16,000
Cervid	TX, PA, OH, FL, LA, IA, & KS	$894 (farming) $757 (hunting)	$3,000
Meat Goats	TX, TN, CA, GA, OK, NC, KY, MO, FL, & AL	$173.2 $189 (breeding)	$1,039
Dairy Goats	TX, OH, NY, PA, WI, WA, IN, CA, MD, MN, MI, FL, & KS.	$58.3 $14.8 (export)	$439
Sheep	TX, CA, WY & CO	$750	$4,500
Catfish/Aquaculture	**Catfish** MS, AK, AL, & LA **Trout** WA, WI, PA, ID, NC, OR, NY, CA, & CO	Catfish $480 Trout $87.5	$2,880 $159
	Total =	**$4,407**	**$33,848**

NADA Approvals for Minor or Specialty Species

- Costly and time consuming
  - Efficacy
  - Target animal safety
  - Human food safety
  - Environmental assessment
- Estimated cost to add an additional claim to a drug label for a pharmaceutical company is $10 to $25 million.
- Over the years, the cost for MUADP to provide information to support a single label claim has risen to approximately $3.1 million (~12 to 30% of cost to pharma).
- Economic incentive is lacking for pharmaceutical companies due to poor return on investment.

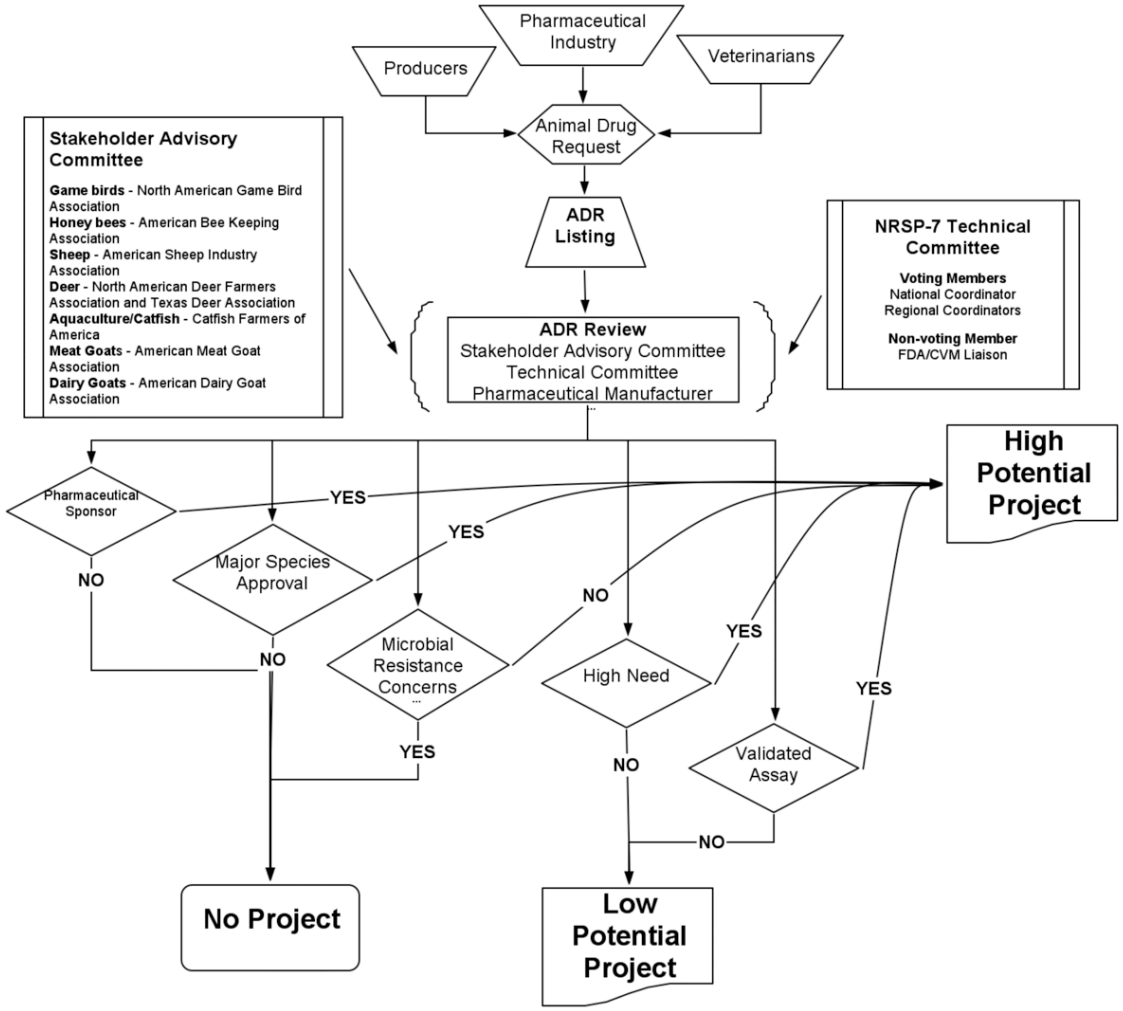
Operational Flowchart



Stakeholder Advisory Committee

- Game birds - North American Game Bird Association
- Honey bees - American Bee Keeping Association
- Sheep - American Sheep Industry Association
- Deer - North American Deer Farmers Association and Texas Deer Association
- Meat Goats - American Meat Goat Association
- Dairy Goats - American Dairy Goat Association
- Aquaculture/Catfish - Catfish Farmers of America

Prioritization of Research



Approvals and Activity by Industry

Industry	Activity	
	Approvals	Active Projects
Game Bird	**Chukar partridges** Sulfadimethoxine/Ormetoprim Lasalocid **Pheasants** Amprolium Thiabendazole **Quail** Salinomycin Bacitracin Monensin	**Pheasants** Lasalocid Sulfadimethoxine/Ormetoprim Fenbendazole
Rabbits	Lasalocid	Ivermectin
Honey Bees	Tylosin	Lincomycin
Cervid	**Bison** Ivermectin **Reindeer** Ivermectin	**Deer** Lasalocid **Fallow Deer** Fenbendazole
Meat Goats	Fenbendazole Monensin Decoquinate Morantel tartrate	Lasalocid CIDR (progesterone) Tulathromycin
Dairy Goats	Fenbendazole Monensin Decoquinate Morantel tartrate	Lasalocid CIDR (progesterone) Ceftiofur HCl (Intramammary) Tulathromycin
Sheep	**Bighorn Sheep** Fenbendazole **Sheep** Decoquinate Ceftiofur Tilmicosin phosphate CIDR (progesterone)	**Sheep** Tulathromycin
Catfish/Aquaculture†	**Catfish** Sulfadimethoxine/Ormetoprim **Finfish** Formalin Oxytetracycline Hydrogen peroxide **Lobster** Oxytetracycline	**Fish** Sulfadimethoxine/Ormetoprim Florfenicol Erythromycin Oxytetracycline Strontium chloride **Shrimp** Florfenicol

†Approvals resulted in an additional 16 label claims for these aquatic species.

Accomplishments

- 36 Public Master Files have been published during the 28 years of the program - 1.3 approvals per year.
- Mean expenditure per approval is approximately $3.1 million vs $10 to $25 million cost to industry.
- 147 peer-reviewed publications.

MINOR USE ANIMAL DRUG PROGRAM PEER-REVIEWED PUBLICATIONS (1983 – 2009)

(1) Spitsbergen, J. M., Blazer, V. S., Bowser, P. R., et al. Finfish and aquatic invertebrate pathology resources for now and the future. *Comp Biochem Physiol C Toxicol Pharmacol* **2009**, *149*, 249-57.

(2) Wesley, I. V., Larsen, S., Hurd, H. S., McKean, J. D., Griffith, R., Rivera, F., Nannapaneni, R., Cox, M., Johnson, M., Wagner, D., and de Martino, M. Low prevalence of Listeria monocytogenes in cull sows and pork. *J Food Prot* **2008**, *71*, 545-9.

(3) Smith, G. W., Davis, J. L., Tell, L. A., Webb, A. I., and Riviere, J. E. Extralabel use of nonsteroidal anti-inflammatory drugs in cattle. *J Am Vet Med Assoc* **2008**, *232*, 697-701.

(4) Hurd, H. S., Brudvig, J., Dickson, J., Mircetu, J., Polovinski, M., Matthews, N., and Griffith, R. Swine health impact on carcass contamination and human foodborne risk. *Public Health Rep* **2008**, *123*, 343-51.

(5) Hawkins, M. G., Taylor, I. T., Craigmill, A. L., and Tell, L. A. Enantioselective pharmacokinetics of racemic carprofen in New Zealand white rabbits. *J Vet Pharmacol Ther* **2008**, *31*, 423-30.

(6) Groocock, G. H., Grimmett, S. G., Getchell, R. G., Wooster, G. A., and Bowser, P. R. A survey to determine the presence and distribution of largemouth bass virus in wild freshwater bass in New York State. *J Aquat Anim Health* **2008**, *20*, 158-64.

(7) Bartlett, S. L., Wooster, G. A., Sokolowski, M. S., Dove, A. D., and Bowser, P. R. Naturally occurring bacteraemia in American lobsters, Homarus americanus Milne-Edwards, in Long Island Sound. *J Fish Dis* **2008**, *31*, 19-25.

(8) Needham, M. L., Webb, A. I., Baynes, R. E., Riviere, J. E., Craigmill, A. L., and Tell, L. A. Current update on drugs for game bird species. *J Am Vet Med Assoc* **2007**, *231*, 1506-8.

(9) Kosoff, R. E., Chen, C.-Y., Wooster, G. A., Getchell, R. G., Clifford, A., Craigmill, A. L., and P.R., B. Sulfadimethoxine and Ormetoprim Residues in Three Species of Fish After 5-day Oral Dosing in Feed. *J. Aquatic Animal Health* **2007**, 109-115.

(10) Getchell, R. G., Groocock, G. H., Schumacher, V. L., Grimmett, S. G., Wooster, G. A., and Bowser, P. R. Quantitative polymerase chain reaction assay for largemouth bass virus. *J Aquat Anim Health* **2007**, *19*, 226-33.

(11) Chen, C.-Y., Chao, C.-B., and Bowser, P. R. Comparative histopathology of Streptococcus iniae and Streptococcus agalactiae infected tilapia. . *Bull European Assoc Fish Pathologists* **2007**, *27*, 2-9.

(12) Payne, M. A., Craigmill, A., Riviere, J. E., and Webb, A. I. Extralabel use of penicillin in food animals. *J Am Vet Med Assoc* **2006**, *229*, 1401-3.

(13) Chen, C.-Y., Chao, C.-B., and Bowser, P. R. Infection of tilapia Oreochromis sp. by Vibrio vulnificus in freshwater and low salinity environments. . *J. World Aquaculture Soc* **2006**, *37*, 82-88.

(14) Wooster, G. A., Martinez, C. M., Ohara, D. S., and Bowser, P. R. Human Health Risks Associated with Formalin Treatments Used in Aquaculture: Initial Study. *North American J. Aquaculture* **2005**, *67*, 111-113.

(15) Tort, M. J., Hurley, D., Fernandez-Cobas, C., Wooster, G. A., and Bowser, P. R. Effects of hydrogen peroxide treatment on catalase and glutathione activity in walleye (Sander vitreus). . *J. World Aquaculture Soc* **2005**, *36*, 577-586.

(16) Smith, G. W., Gehring, R., Craigmill, A. L., Webb, A. I., and Riviere, J. E. Extralabel intramammary use of drugs in dairy cattle. *J Am Vet Med Assoc* **2005**, *226*, 1994-6.

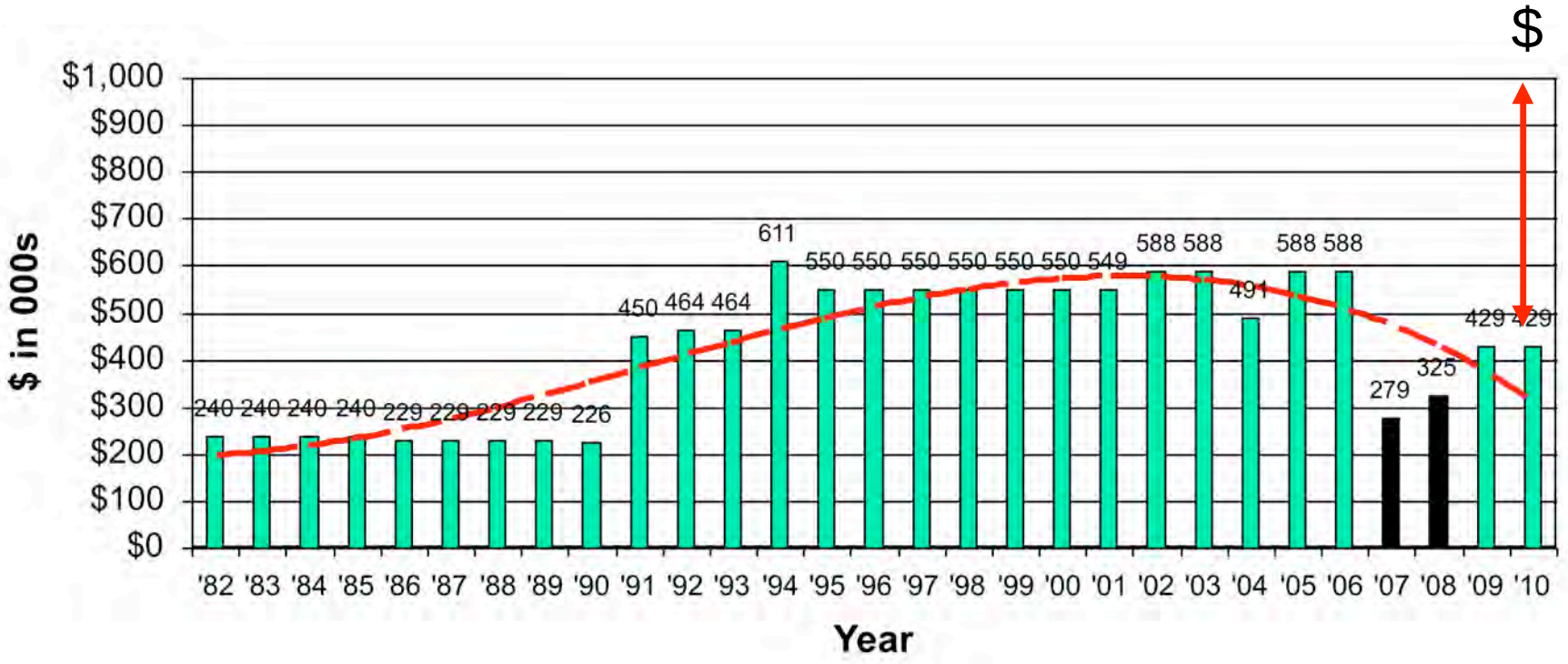
Currently 17 Active Projects

DRUG	FORMULATION	SPECIES	INDICATION	INAD
Erythromycin	Premix	Fish (Salmonids)	Bacterial kidney disease	6013
Fenbendazole	Premix	Deer	GI parasites	10-993
Fenbendazole	Premix	Pheasants & partridges	Gapeworm	10-062
Florfenicol	Oral	Fish (finfish)	Bacterial infection	11-145
Florfenicol	Injection	Sheep	Respiratory infections	10-958
Ivermectin	Injectable	Rabbits	Ear mites	9557
Lasalocid	Premix	Deer	Coccidiosis	10-746
Lasalocid	Premix	Goats	Coccidiosis	10-872
Lasalocid	Premix	Pheasants	Coccidiosis	9096
Lincomycin	Soluble powder	Honey Bees	American Foulbrood	10-776
Oxytetracycline	Feed	Fish (Various)	Vibriosis	10-320
Progesterone	CIDR	Goats	Estrus synchronization	11-389
Progesterone	CIDR	Sheep	Estrus synchronization	10-321
Strontium chloride	Immersion	Fish	Otolith marking	10-536
Sulfadimethoxine & ormetoprim	Premix	Fish	Bacterial infections	10-823
Tulathromycin	Injection	Goats	Respiratory infection	11-512
Tulathromycin	Injection	Sheep	Respiratory infection	11-513

Forty Potential Projects

ADR	Drug	Formulation	Species	Indication
209	Amoxicillin	Premix	Salmonids	Furunculosis
270	Amoxicillin	Premix	Hybrid striped bass	Strep infections
176	Amoxicillin	Injectable	Dairy goats (lactating)	Bacterial pneumonia
198	Ceftiofur	Injectable	Rabbits	Pasteurellosis
251	Ceftiofur	Injectable	Deer, red	Respiratory infections
228	Ceftiofur	Injectable	Veal calves	Respiratory infections
236	Clopidol	Premix	Pheasant	Coccidiosis
231	Copper sulfate	Topical soluble powder	Catfish, channel	External protozoan parasites
281	Deccox	Premix	Pheasants	Coccidiosis
281	Deccox	Premix	Partridges	Coccidiosis
174	Erythromycin	Premix/ injectable	Salmonids	Bacterial kidney disease
325	Florfenicol	Injectable	Sheep	Respiratory infections
326	Florfenicol	Injectable	Sheep	Foot rot
327	Florfenicol	Injectable	Goats	Respiratory infections
328	Florfenicol	Injectable	Goats	Foot rot
260	Hydrogen peroxide	Topical	Atlantic salmon	Sea lice
312	Imidocarb	Injectable	Dairy cattle	Anaplasmosis babesiosis
222	Ivermectin	Pour-on	American bison	GI parasites
197	Ivermectin	Pour-on	Deer, red	GI parasites and lungworm
341	Melatonin	Implant	Sheep	Reproductive aid
336	Metomidate	Injectable	Ornamental fish	Anesthesia
284	MGA/GnRH	Feed/ injectable	Sheep	Estrus synchronization
342	Moxidectin	Oral	Goats	Internal parasites
273	Nitarsone	Premix	Partridge	Blackhead
66	Novobiocin/ penicillin	Intramammary infusion	Dairy goats	Mastitis
335	Ovaprim	Injectable	Ornamental fish	Spawning aid
120	Oxolinic acid	Premix	Salmonids	Furunculosis, vibriosis
332	Oxytetracycline	Oral	Abalone	Withering syndrome
19	Oxytetracycline	Premix	Alligators	Bacterial infection
43	Oxytetracycline	Injectable	Dairy goats (nonlactating)	Bacterial pneumonia
161	Oxytetracycline	Premix	striped bass	Pasteurellosis
286	Oxytetracycline	Feed	Tilapia	Strep infections
299	Pirlimycin	Intramammary	Goats	Mastitis
277	Potassium permanganate	Topical	Catfish	External *ichthyophthirius multifilis*
31	Praziquantel	Premix/ oral capsule	Ducks, geese, swan	Schistosomiasis
343	Remebee	Oral	Honey bees	Israeli Acute Paralysis Virus
178	Spectinomycin	Injectable/oral	Ducks	Colibacillosis, salmonellosis
74	Sulfamethazine	Oral sustained release	Sheep	Bacterial pneumonia
138	Virginiamycin	Premix	Alligators	Hatchling alligator syndrome
274	Zoamix	Premix	Pheasant	Coccidiosis

MUADP Funding by Year



Funding and Anticipated Results

With MUADP total level of funding of approximately $429,000 per year and cost per drug approval of $3.1 million, the expected time for achieving a drug approval is 7 years.

Balancing several studies over each year, it is anticipated that MUADP will achieve **one** approvals over the next **five** years.

Looking Forward – Draxxin®

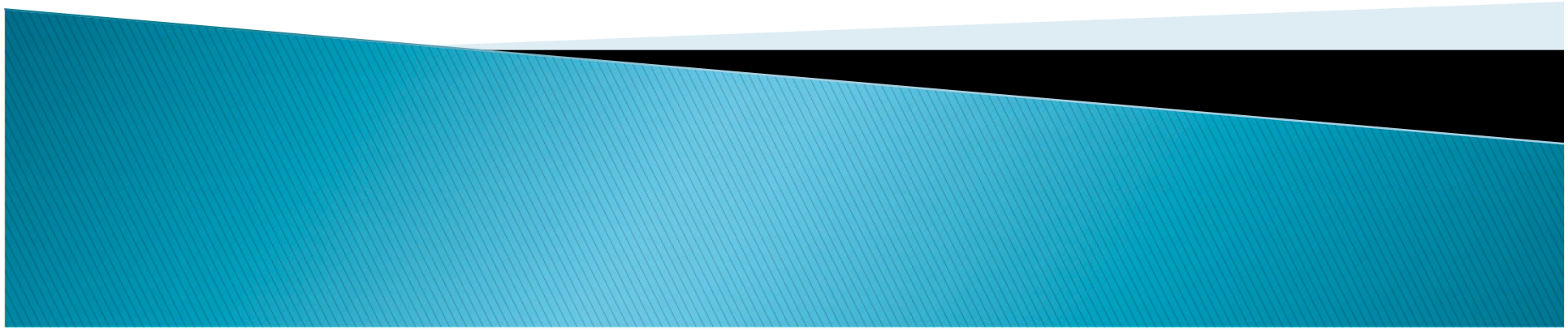
APPENDIX III
PRESENTATION OF PROJECTS OF INTEREST TO PFIZER

Minor Use Animal Drug Program

North Central Region Report

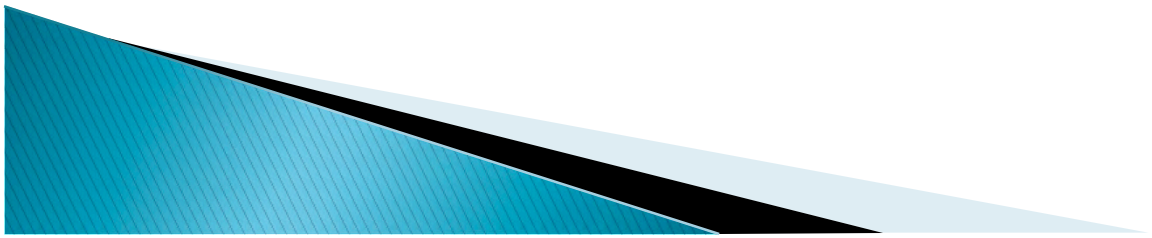
R. W. Griffith

Department of Veterinary Microbiology and Preventive Medicine, Iowa State University



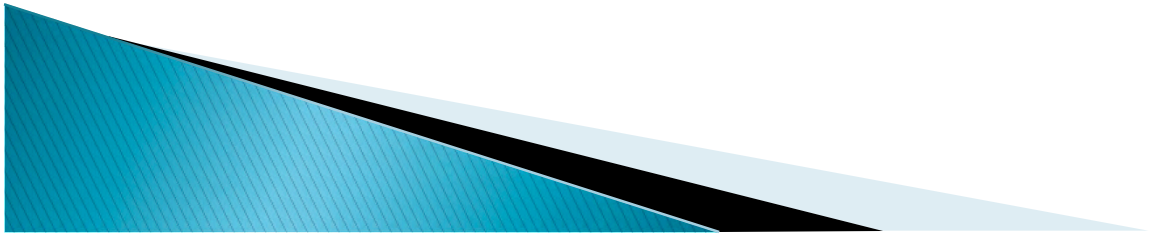
Projects of Interest to Pfizer

- CIDR intravaginal implants in goats for synchronization of estrus
- Tulathromycin for use in goats and sheep



HFS CIDR-G in Goats

- Milk residue study report was accepted.
- Zero-day withdrawal for milk approved by FDA/CVM
  - This is allowing us to perform the efficacy trials in milk goats this fall without discarding milk.



CIDR-G Tissue Residues

- Study report has been submitted
- 12 does
- 6 Controls and 6 CIDR-Treated
- 18 day CIDR-Treatment
- Remove CIDR's
- Collect tissues 8 – 12 h after CIDR removal

Control Group P4 Residues

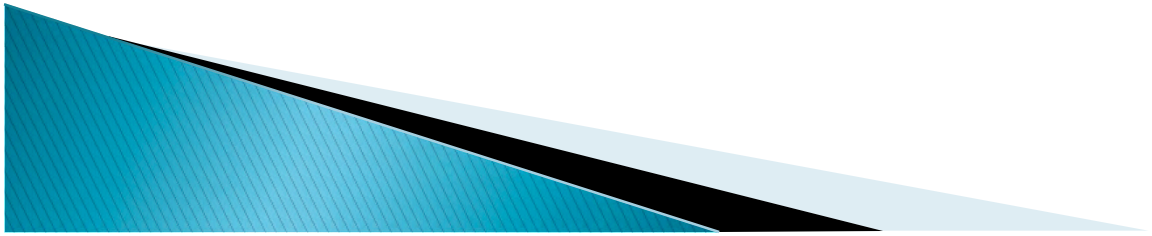
Animal #	Muscle ng/ml	Fat ng/ml	R. Ovary	L. ovary
04	7.4	190	Early CL	Early CL
24	1.0	13.4	No significant structures	Immature follicle
31	6.0	496	CL, old but functional	CL, old but functional
1677	0.9	0.9	Pre-ovulatory follicle	Pre-ovulatory follicles (2 – 3)
366	11.4	279	CL, 7 – 8 d old	CL, 7 – 8 d old
578	10,0	352	Old CL	Old CL
Mean	6.1 $\pm$ 1.8	222 $\pm$ 79.3		

P4 Residues 8-12 hr after Removal of CIDR-G

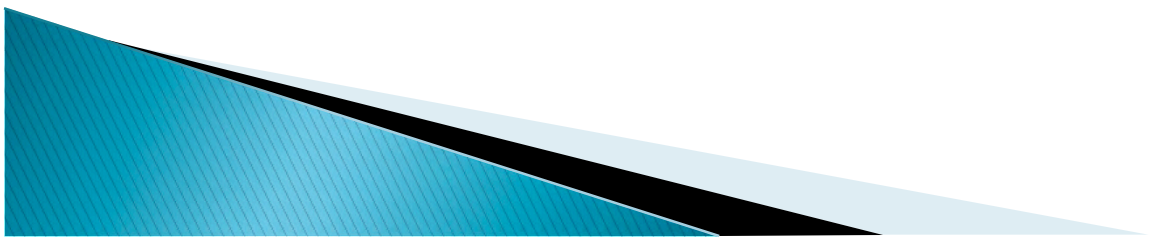
Animal #	Muscle ng/ml	Fat ng/ ml	R. Ovary	L. ovary
681	1.8	5.8	Pre-ovulatory follicle CL>14d	Pre-ovulatory follicles
859	0.8	10.7	No significant structures	Pre-ovulatory follicles (2-3)
343	0.4	9.8	Pre-ovulatory follicle	Pre-ovulatory follicle
8937	0.9	5.4	Pre-ovulatory follicle	Pre-ovulatory follicles
45	0.7	5.4	Pre-ovulatory follicle	No significant structures
50	0.5	4.5	No significant structures	No significant

CIDR-G Efficacy in Goats

- Meat goat herds
  - 174 in Iowa
  - 135 at Texas A&M Prairieview
  - Need more
- Dairy goat herds
  - 45 does at Davis
  - 240 does in Iowa
  - 60 does in Wisconsin
  - 64 does in Minnesota
  - 200 does in Missouri



Draxxin in Goats



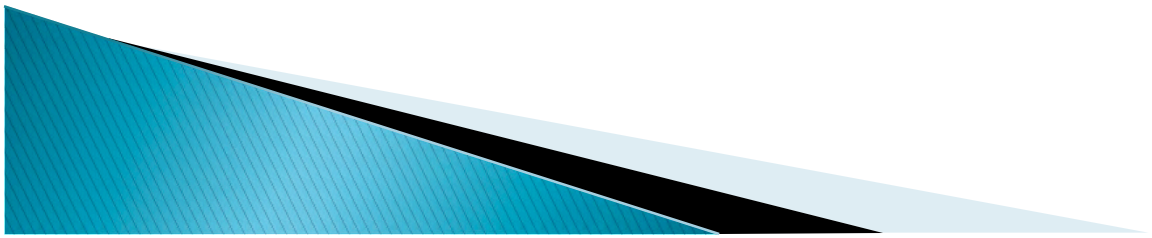
Draxxin in Goats

- Target Animal Safety study report has been submitted to FDA/CVM.
- Review by July-August
- Paper has been accepted for publication

Draxxin TAS Goat Facilities

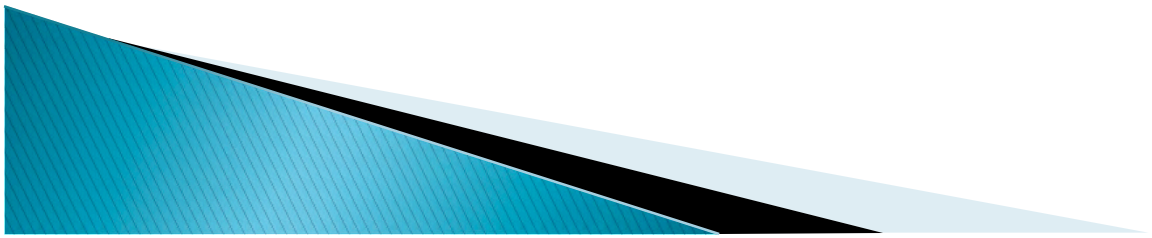
Human Food Safety of Draxxin in Goats

- Tissues were collected at 5, 12, 18, 25 and 48 days following subcutaneous administration of the label dose of Draxxin.
- Tissues were shipped to the Western Region lab in early November, 2009.
- Study report is nearing completion
- Paper submitted for publication



Draxxin Efficacy: A Study in Patience

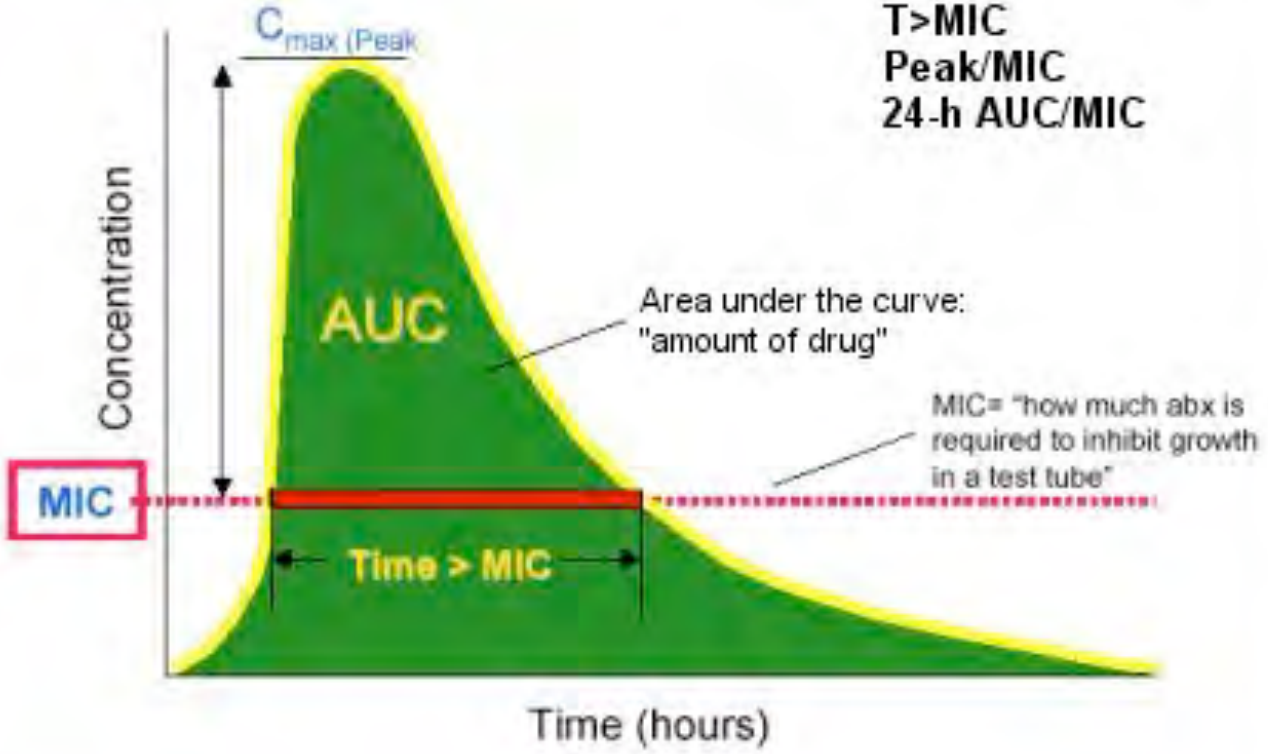
- AUC/MIC approach was performed at the suggestion of ONADE.
- Draxxin given subcutaneously was very rapidly absorbed (Similar to other animal species).
- Plasma analysis has been completed.



Pharmacokinetic/Pharmacodynamic Predictors of Efficacy

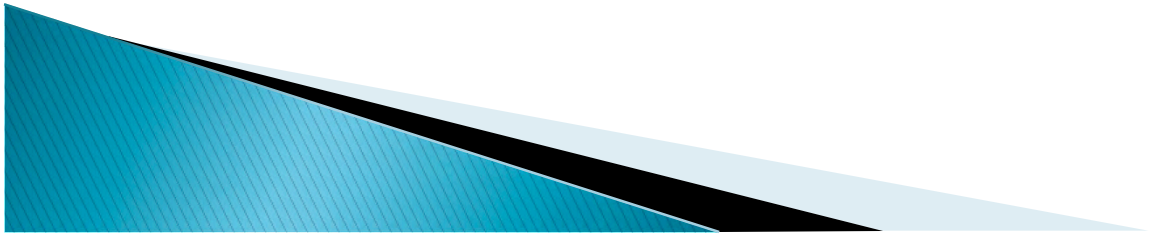
PK/PD parameters

T>MIC
Peak/MIC
24-h AUC/MIC



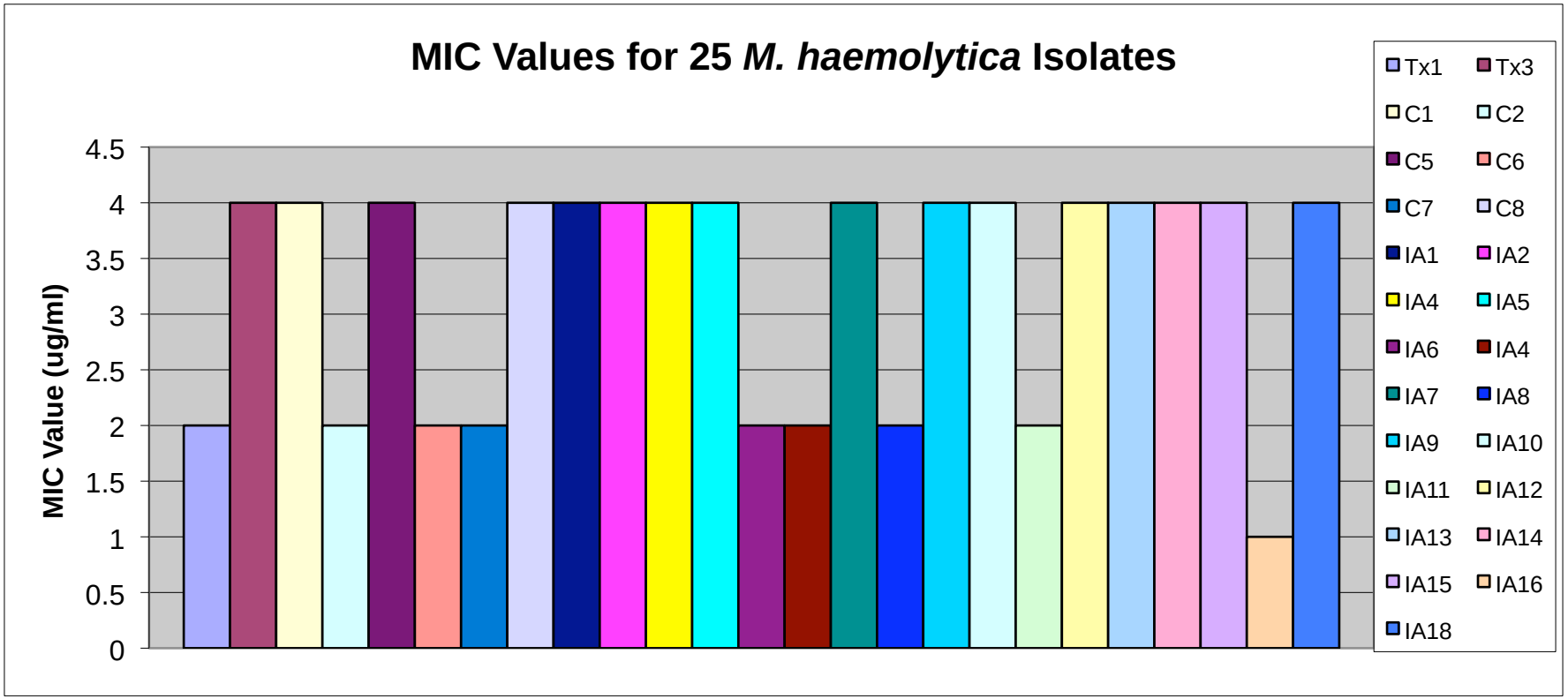
MIC's

- *Mannheimia haemolytica*, *Pasteurella multocida, Bibersteinia trehalosi* and *Mycoplasma* species werecollected for MIC data.
- Sufficient isolates of *M. haemolytica* wre collected and MIC's determined.



Results

Isolates collected from different regions of the U.S.

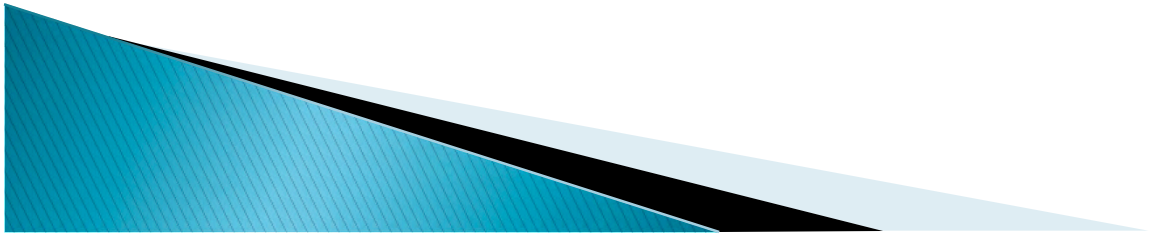


Average MIC = 3.4

Measured at ug/ml for this antimicrobial

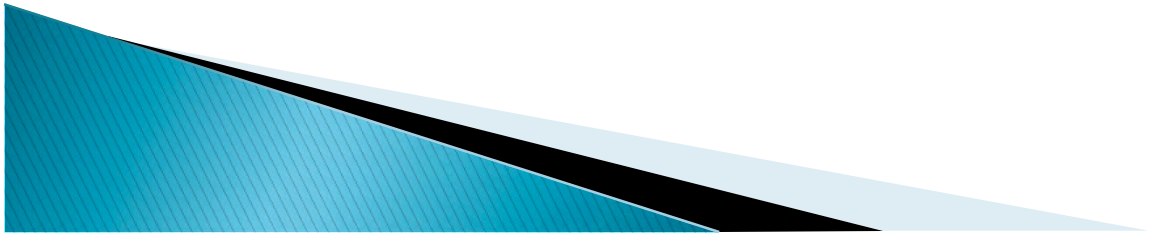
Killing Kinetics

- Product development conference with ONADE in March 2010.
- It was suggested that we gather killing kinetics data on our bacterial isolates.
  - Completed in July, 2010



New Suggestion

- Alveolar Macrophages
  - Demonstrate similar concentrations of tulathromycin in pulmonary macrophages of cattle, goats and sheep.



APPENDIX IV
ANTIMICROBIAL GUIDANCE DOCUMENT #152

152

Guidance for Industry

Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern

This document discusses a recommended approach for assessing the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern.

Comments and suggestions regarding this document should be sent to the Division of Dockets Management (HFA 305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the Docket No.98D-1146. Submit electronic comments to http://www.fda.gov/dockets/ecomments.

Direct questions regarding this document to Jeffrey M. Gilbert, (HFV-157), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-0233, e-mail: jgilbert@cvm.fda.gov.

Additional copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855 and may be viewed on the Internet at http://www.fda.gov/cvm.

Paperwork Reduction Act Public Burden Statement
According to the Paperwork Reduction Act of 1995, a collection of information should display a valid OMB control number. The valid OMB control number for this information collection is 0910-0522 (Expires 4/30/05). The time required to complete this information collection is estimated to average 1,084 hours per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
October 23, 2003

Table of Contents

Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern[1]

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statute and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing the guidance. If you cannot identify the appropriate staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

Prior to approving an antimicrobial new animal drug application, FDA must determine that the drug is safe and effective for its intended use in the animal. The Agency must also determine that the antimicrobial new animal drug intended for use in food-producing animals is safe with regard to human health (21 CFR 514.1(b)(8)). FDA considers an antimicrobial new animal drug to be "safe" if it concludes that there is reasonable certainty of no harm to human health from the proposed use of the drug in food-producing animals. This document provides guidance for industry on a possible process for evaluating the potential effects of antimicrobial new animal drugs on non-target bacteria as part of the new animal drug application process.

This guidance document outlines a risk assessment approach for evaluating the microbial food safety of antimicrobial new animal drugs. Within the context of risk assessment, many possible mechanisms to address the development of antimicrobial resistance resulting from the use of antimicrobial new animal drugs in food-producing animals are available to the sponsor. Alternative processes that may be more appropriate to a sponsor's drug and its intended conditions of use, may be used to characterize the microbial food safety of that drug.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as guidance, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Human Food Safety, Office of New Animal Drug Evaluation, Center for Veterinary Medicine (CVM), at the Food and Drug Administration.

II. SCOPE OF GUIDANCE DOCUMENT

As part of the pre-approval safety evaluation process, FDA intends to consider the potential impact on human health of all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals. The scope of this document is an assessment of the effect of the transmission of foodborne bacteria of human health concern through the consumption of animal derived food products. Although FDA's primary focus will be foodborne pathogens, other (enteric/gastrointestinal) bacteria may be considered when deemed necessary.

Further clarification is provided regarding microbial food safety considerations that should be addressed, and the investigational new animal drugs (INADs) or new animal drug applications (NADAs) covered by the guidance described herein. This document focuses on the concern that the use of antimicrobial new animal drugs in food-producing animals will result in the emergence and selection of antimicrobial resistant food-borne bacteria which impact human health adversely.

Note: Effects of drug residues on human intestinal microflora: Antimicrobial drug residues present in food from food-producing animals may cause adverse effects on the ecology of the intestinal microflora of consumers.[1, 2] For further information on requirements regarding these effects, refer to FDA Guidance for Industry #52 entitled "Assessment of the Effects of Antimicrobial Drug Residues from Food of Animal Origin on the Human Intestinal Flora."

The FDA believes that human exposure through the ingestion of antimicrobial resistant bacteria from animal-derived foods represents the most significant pathway for human exposure to bacteria that have emerged or been selected as a consequence of antimicrobial drug use in animals.

This risk assessment approach is recommended for all uses of all antimicrobial new animal drugs in food-producing animals; however, sponsors of applications described below are encouraged to consult with FDA to decide if the risk assessment approach is recommended for their application.

1. **Certain supplemental NADAs:** Microbial food safety information is not typically needed for Category I supplemental NADAs (21 CFR 514.106(b)(1)). These supplements ordinarily do not require a reevaluation of any of the safety or

effectiveness data in the parent application. However, information may be needed for certain Category II supplemental NADAs (21 CFR 514.106(b)(2)). These supplements may require a re-evaluation of certain safety or effectiveness data in the parent application.

2. **NADAs for antimicrobial drug combinations:** Microbial food safety information would ordinarily not be needed for antimicrobial drug combinations as defined in Section 512(d) of the Act (21 U. S. C. 360b(d)), as amended by the Animal Drug Availability Act (ADAA) of 1996. Microbial food safety would typically be addressed as part of the NADAs for the individual antimicrobial drugs that comprise the combination. However, in certain circumstances information may be requested for drug applications for antimicrobial drug combinations.

3. **Abbreviated (generic) NADAs:** Microbial food safety information would not be needed for abbreviated new animal drug applications (ANADAs) filed under section 512(b)(2) of the Act for generic copies of approved antimicrobial new animal drugs. Microbial food safety information would be needed for supplements to add claims to approved ANADAs.

III. RISK ANALYSIS METHODOLOGY

This guidance document outlines a risk analysis method, and describes its application as a process for evaluating human food safety with respect to the potential microbiological effects of antimicrobial new animal drugs on food-borne bacteria of human health concern. The sponsor of an antimicrobial new animal drug may use this guidance and the methodology described herein to conduct a qualitative risk assessment as part of the pre-approval safety evaluation of a new animal drug. It is important to note that the sponsor is free to demonstrate the safety of their proposed drug product in other ways.

FDA's current thinking on a qualitative approach for risk assessment, especially where there may be a lack of substantial data, is described in this guidance. FDA does not intend to exclude quantitative risk assessment in favor of a qualitative process. Further, FDA encourages sponsors to seek data and modeling approaches that can best refine and improve the approach and assumptions incorporated in this risk assessment process.

If the sponsor elects to use this or a similar process, FDA recommends the assessment be submitted to the INAD file with supporting data as a component of the Human Food Safety technical section, or should be included in the NADA as part of the sponsor's submission under 21 CFR 514.1(b)(8). The results of this risk assessment can help to estimate the overall risk, allowing an informed risk management decision. Evaluation of all available information submitted in support of the NADA may result in actions ranging from approval of the new animal drug to denial of the new animal drug application. The remainder of the document provides guidance on this risk analysis method.

A. Background:

The risk analysis process outlined in this document is based on the process described by the Office International des Epizooties (OIE) Ad Hoc Group on Antimicrobial Resistance.[3] The OIE risk analysis methodology is tailored to address antimicrobial resistance in animals and includes hazard identification, risk assessment, risk management, and risk communication. Although the OIE approach differs organizationally from the risk analysis paradigm described by the National Academy of Science/National Research Council (NAS/NRC), the OIE process includes similar steps to describe the risk assessment.[4]

The risk assessment process described in this guidance is comprised of a hazard characterization, a release assessment, an exposure assessment, a consequence assessment, and a risk estimation (See Figure 1). The risk estimation integrates the components of the risk assessment into an overall conclusion, providing a qualitative indication of the potential risk to human health of the proposed use of the antimicrobial new animal drug. FDA then uses the overall risk estimation ranking, along with other relevant data and information submitted in support of the NADA, to determine whether the drug is approvable under specific risk management conditions.

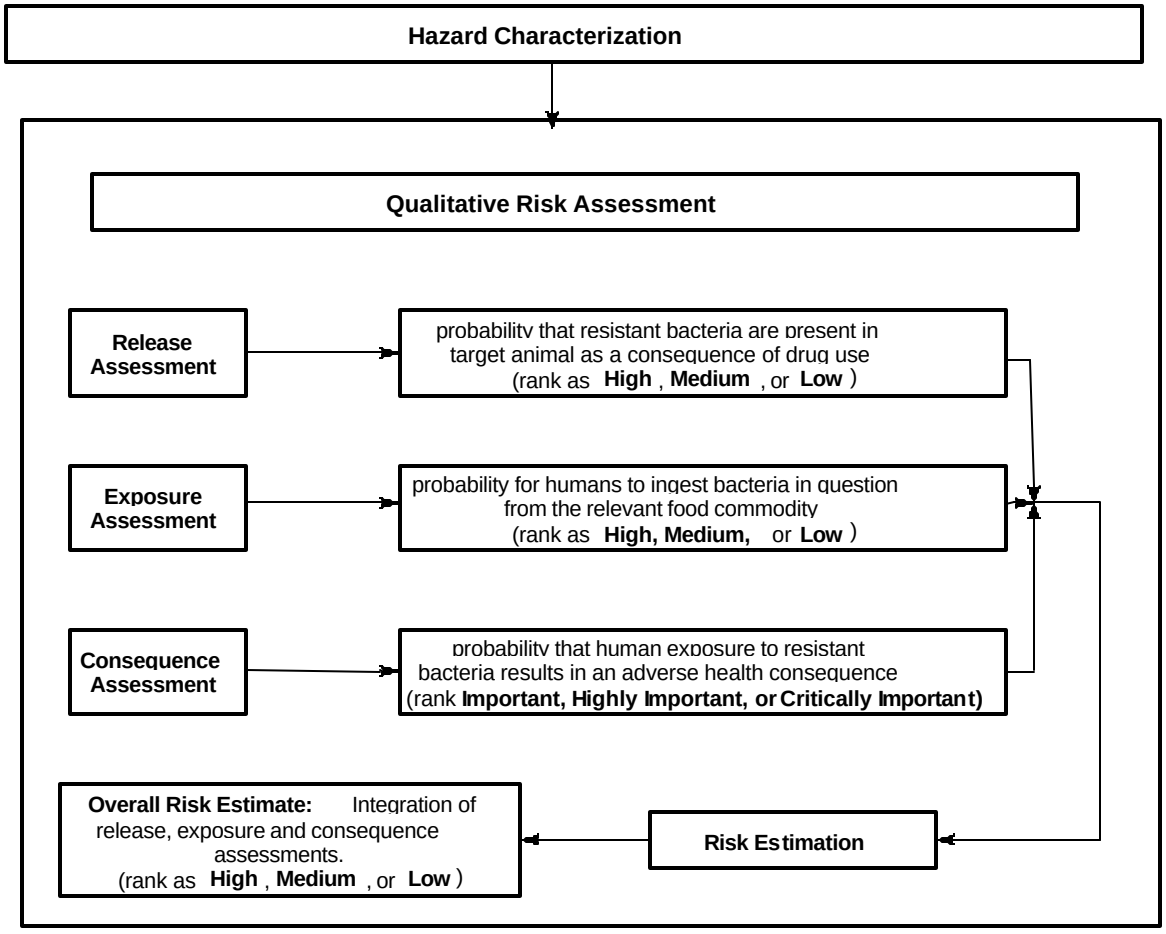


Figure 1: Components of a qualitative antimicrobial resistance risk assessment

B. Definitions:

1. Hazard: Human illness, caused by an antimicrobial-resistant bacteria, attributable to an animal-derived food commodity, and treated with the human antimicrobial drug of interest.

2. Hazardous agent: Antimicrobial-resistant food-borne bacteria of human health concern that are in or on a food-producing animal as a consequence of the proposed use of the antimicrobial new animal drug.

3. Risk: The probability that human food-borne illness is caused by an antimicrobial-resistant bacteria, is attributable to an animal-derived food commodity, and is treated with the human antimicrobial drug of interest.

   FDA's overriding concern is the decreased or lost effectiveness of antimicrobial drugs in humans as a consequence of human exposure to resistant bacteria through ingestion of animal derived food products. FDA is concerned about a range of deleterious effects that antimicrobial resistant bacteria may have on human health. These effects include but are not limited to increased duration of illness, treatment failure, and loss of therapeutic options. Due to the difficulties associated with measuring loss of effectiveness, the risk assessment process described in this guidance document estimates the probability of the occurrence of the hazard.

C. Data sources/data quality:

A variety of materials may be used to support a microbial food safety assessment. These materials should meet FDA standards for data used to support an approval. Sponsors may consider:

1) Generating necessary data through the conduct of prospective studies. FDA recommends that drug sponsors refer to 21 CFR Part 58 for requirements related to Good Laboratory Practices for conducting non-clinical laboratory studies.

2) Submission of current and relevant literature (including peer reviewed, published literature). FDA recommends that sponsors refer to Guidance for Industry #106,

"The Use of Published Literature in Support of New Animal Drug Approval" for guidance regarding use of published literature.

IV. HAZARD CHARACTERIZATION

Note: Prior to initiating and submitting the risk assessment, FDA recommends that sponsors electing to use this process characterize the hazard, and the conditions that influence the occurrence of that hazard. CVM envisions hazard characterization as distinct and separate from the qualitative risk assessment and it is recommended that the hazard characterization be submitted to the FDA as a stand alone document. This submission will enable the sponsor and the FDA to determine the information that should be included in the risk assessment. In addition, based on the hazard characterization, it may be determined in certain cases that completion of a risk assessment is not recommended.

The hazard has been defined as human illness, caused by an antimicrobial-resistant bacteria, attributable to an animal-derived food commodity, and treated with the human antimicrobial drug of interest.

FDA recommends that sponsors address the hazard characterization step of the risk assessment by submitting information regarding the chemical, biochemical, microbiological, and physical properties of the antimicrobial new animal drug that bear on characterizing the downstream effects of the drug. This information may include, but should not be limited to:

A. Drug-specific information:

Chemical name and structure

1. Class of antimicrobial drug (e.g., macrolide)

2. Mechanism (e.g., protein synthesis inhibitor) and type of action (i.e., bactericidal vs. bacteriostatic)

3. Spectrum of activity (e.g., Gram-positive, Gram-negative, broad, or narrow spectrum, etc.)

4. Standardized antimicrobial susceptibility testing methodology *and* specific susceptibility data (i.e., minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) data pertinent to the appropriate bacteria of human health concern). FDA recommends that if the sponsor does not use standardized susceptibility test methods, the sponsor should include a detailed description of the antimicrobial susceptibility testing method(s) used for determining the susceptibility of the bacterial isolates of concern and the reason(s) for the needed change. The

methods should include the quality control organism(s), the dilution scheme used, and the source for the interpretive criteria for human or veterinary isolates. The methods may include citations, if available, of relevant laboratory standards such as the National Committee on Clinical Laboratory Standards (NCCLS). Additional guidance on susceptibility testing may be obtained from recognized sources such as NCCLS documents.

5. Relative importance of the drug in human medicine (see Appendix A).

B. Bacterial resistance information:

Taking into account the target animal species to be treated with the drug, the conditions of intended animal use of the drug in animals, and the antimicrobial properties of the drug in question, FDA recommends that the sponsor identify:

1. Bacterial species and strains for which resistance acquisition has potential human health consequence.

2. Known resistance determinants or mechanisms associated with the antimicrobial drug(s) of interest. FDA recommends that information describing phenotypic and genotypic similarities with resistance determinants in other food-borne bacteria of human concern be identified.

C. Data gaps and emerging science: The sponsor or FDA may identify data gaps and areas of emerging science that may be relevant to the microbial food safety assessment for the proposed conditions of use.

V. QUALITATIVE RISK ASSESSMENT

Note: After submission and review of the hazard characterization, and prior to completing the risk assessment, the sponsor may wish to consult with FDA regarding recommendations on additional information to complete the risk assessment.

The OIE method is described below in a simplified format. The risk assessment approach is comprised of a release assessment, an exposure assessment, a consequence assessment, and a risk estimation (refer to Figure 1).

FDA recommends that sponsors adapt and expand their risk assessment to accommodate the unique relationships that may exist among an antimicrobial new animal drug, affected microbe(s), proposed condition(s) of use, and other parameters that potentially affect human health. The assessment process outlined below will result in an overall estimate of the level

of concern (risk estimation) associated with the emergence or selection of resistant bacteria as a consequence of the proposed use of the drug in animals. This process may help guide the selection of appropriate risk management steps.

Note: FDA intends to determine the appropriate use conditions or other risk management steps based on its review and consideration of the new animal drug application as a whole, including any risk assessment submitted by the sponsor as part of the application.

A. Release Assessment:

The release assessment estimates the probability that the proposed use of the antimicrobial new animal drug in food-producing animals will result in the emergence or selection of resistant bacteria in the animal.

1. Defining the boundaries of the release assessment:

   The boundaries of the release assessment span from the point the antimicrobial new animal drug is administered to the food-producing animal, to the point the animal is presented for slaughter or the animal-derived food is collected.

   For the purposes of this guidance, FDA is focusing on the food-producing animal as the source of human exposure to the hazardous agent. Human exposure to the hazardous agent should be addressed in the exposure assessment.

2. Factors that may be considered in release assessment:

   A number of relevant factors are suggested for consideration in completing the release assessment. These factors include items that are also considered as part of the hazard characterization step described earlier.

   Note: Following submission of the hazard characterization, the sponsor may wish to consult with FDA to determine the specific factors most relevant to the proposed conditions of use of the antimicrobial new animal drug in question.

   In order to address specific considerations pertinent to the drug and its proposed conditions of use, the sponsor or FDA may consider factors not listed below. The relative significance of any particular factor may vary depending on the specific antimicrobial new animal drug application under consideration. Therefore, when determining the overall release assessment ranking, certain factors may carry greater weight than other factors. FDA recommends that the factors considered in the release assessment include the following. Other factors may also be relevant. FDA recommends these be clearly defined and supported.

a. Product description:

- Product formulation (active and inactive ingredients)
- Information regarding proposed conditions of use including:
  - Route of administration (i.e., injection, water, feed)
  - Dosing regimen
  - Proposed product indication
  - Intended target animal species
  - Proposed withdrawal time

b. Drug substance description:

- Class of antimicrobial drug (e.g., macrolide)
- Chemical name, CAS number, and structure

c. Mechanism and type of antimicrobial action:

- Specifics regarding antimicrobial mechanisms (e.g., protein synthesis inhibitor)
- Type of action (e.g., bactericidal action vs. bacteriostatic)

d. Spectrum of activity:

- General information (e.g., is active against Gram-positive, Gram-negative, broad, or narrow spectrum, etc.)
- Specific susceptibility data (e.g., minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) data pertinent to the food-borne bacteria of human concern in question)

e. The pharmacokinetics/pharmacodynamics of the drug:

- absorption, distribution, metabolism, and elimination of the drug in the target animal
- data on, or an estimation of, the active antimicrobial drug in colonic contents

- additional effects such as first-exposure effects, post-antibiotic effects, sub-MIC effects, etc.

- Pharmacodynamics, such as concentration and/or time dependent effects, etc.

f. Resistance mechanisms and genetics: FDA recommends that the sponsor provide information regarding the mechanism(s) and genetic basis of resistance development that includes:

- Known mechanism(s) of resistance in animal and human pathogens (e.g., antimicrobial inactivation, alteration of the drug target, reduced uptake, efflux of the antimicrobial drug, etc.)

- Location of resistance determinants (e.g., plasmid-mediated vs. chromosomal; present on transposon, integron, or phage)

g. Occurrence and rate of transfer of resistance determinants: FDA recommends that the sponsor provide information regarding whether resistance determinants are transferable and, if so, at what rate. Relevant questions may include, but are not limited to:

- Can resistance determinants be transferred among bacteria by transformation, transduction, conjugation, or transposition? If so, at what rate?

- If resistance occurs by point mutation, at what rate do the point mutations occur?

h. Resistance selection pressures: FDA recommends that the sponsor provide information to help characterize the relative magnitude of selection pressure for resistance that may exist for the particular drug use in question. Pertinent information may include:

- Information regarding other antimicrobials that may co-select for resistance

- Information regarding cross resistance to other antimicrobial drugs approved in veterinary and human medicine

- Consideration of the extent of use of the proposed product (e.g., duration of administration; individual vs. small groups vs. flocks/herds)

i. Baseline prevalence of resistance: FDA recommends that the sponsor provide available epidemiological data outlining the existing prevalence of resistance to the drug and/or related drugs in target pathogens and commensal gut flora. This

may be obtained from newly generated data, or existing sources of data, such as the National Antimicrobial Resistance Monitoring System (NARMS) data, current literature, or other reliable surveillance sources. If baseline data is not available for the proposed antimicrobial drug, sponsors may wish to consult with FDA regarding collection or generation of such data.

j. Other information relevant to the release assessment:

- Relevant information relating to the rate of resistance development and decline after treatment
- Information or studies to characterize the rate of resistance development in food-borne bacteria of human health concern following use of the drug under the proposed conditions of use.
- Information or studies to characterize the decline of resistance in food-borne bacteria of human health concern following cessation of therapy. Of particular interest is information relative to the interval up to the earliest time point (post-drug administration) at which animals would be presented for slaughter.

3. Summarizing the Release Assessment:

FDA recommends that the sponsor qualitatively characterize all factors relevant to the release assessment based on supporting information. We recommend that this characterization include an estimate of whether each factor would have a high, medium, or low likelihood of favoring resistance emergence. For example, the spectrum of activity of the drug might be ranked high for favoring resistance emergence or selection if the new animal drug in question readily selects for mutations conferring resistance; in contrast, pharmacodynamics might be ranked low with regard to impact on resistance if the drug did not enter the target animal intestinal tract at concentrations shown to have an effect on resistance development, etc. These rankings would then be integrated into an overall release assessment ranking of high, medium, or low. FDA recommends that the sponsor provide a detailed discussion of the conclusions as well as present the conclusions in summary format (see Table 1).

Note: If sufficient information regarding a factor is not available or has not been generated for the assessment, the most conservative estimate (high) of the particular factor should be assumed.

Table 1: Sample table for collating and summarizing interpretation of relevant factors considered in completing the release assessment

Relevant parameters	Extent to which relevant factors favor emergence of resistance	Release[2] (H, M, L)
	Comments/conclusions regarding factors	
Mechanism of activity		
Spectrum of activity		
Pharmacokinetics		
Pharmacodynamics		
Resistance mechanism(s)		
Resistance transfer		
Selection pressure		
Other factors[1]		

[1]Other factors may be identified that are thought to be of importance to the evaluation. After submission of the hazard characterization, the sponsor may wish to consult with FDA regarding additional factors prior to completing the assessment.

[2]Potential for favoring the release of resistant bacteria.

4. Release Assessment conclusion:

   The outcome of the release assessment is intended to estimate the probability that resistant bacteria will emerge or be selected for as a consequence of the proposed drug use in animals. FDA recommends that the sponsor use the conclusions obtained from assessing all relevant factors to derive an overall qualitative ranking for the release assessment. This overall conclusion may be expressed in terms of a high, medium, or low probability that resistant food-borne bacteria will occur in animals as a consequence of the proposed drug use.

B. Exposure Assessment:

The exposure assessment describes the likelihood of human exposure to food-borne bacteria of human health concern through particular exposure pathways, in this case animal derived food products. The exposure assessment should provide a qualitative estimate of the probability of this exposure occurring.

The division of the qualitative risk assessment into "release" and "exposure" components effectively produces a natural placement of animal and animal treatment

factors into the "release assessment component" and food-chain and human factors within the "exposure assessment component." FDA recognizes that there are many factors that may affect the bacteria of interest between the time animals are presented for slaughter (or the animal-derived food is collected) and the time the final food product is consumed.

Note: For the purposes of this qualitative risk assessment, FDA assumes that the probability that bacteria in or on the animal at slaughter may be used as an estimate of the probability of human exposure to that bacterial species in the food commodity derived from that animal.

FDA recognizes that food-borne human exposure to antimicrobial resistant bacteria is complex and often involves the contributions from other sources of exposure (e.g., direct contact between animals and humans, introduction of resistant bacteria and resistance determinants into the environment). However, FDA believes that evaluating antimicrobial new animal drug safety relative to the most significant exposure pathway (i.e., food-borne pathway) is the best way to qualitatively assess the risk of antimicrobial drug use in food-producing animals. Uncertainties regarding the contribution of other exposure pathways may be considered during the development of appropriate risk management strategies.

1. Factors to consider in the exposure assessment:

   The exposure assessment is independent of the use of the antimicrobial drug under review and may be estimated by considering the relative amount of relevant bacterial contamination of the food product and the relative quantity of the food product consumed by humans. While it is acknowledged that other factors such as food preparation practices can affect exposure, the two prior considerations are intended to provide a qualitative indication of the probability of human exposure to the food-borne bacteria of human health concern. Appropriate current survey data of both food commodity contamination and consumption may be submitted to support a qualitative ranking of the probability of human exposure to the given bacteria *via* a particular food commodity.

   FDA recommends that the sponsor derive the exposure assessment ranking by integrating the ranking of the probability of human exposure (through food) to the bacteria in question with the ranking of consumption of the animal derived food commodity. The qualitative probability should be expressed in terms of high, medium, or low as discussed below.

2. Example process for the estimation of exposure to the hazardous agent:

> **Note:** The specific information provided in the tables in this section is for illustrative purposes only. Sponsors may reference a variety of data sources which best characterize human exposure to bacteria of human health concern *via* animal-derived foods. FDA recommends that sponsors reference the most reliable, current data available at the time that the assessment for their product is conducted.

FDA believes that the concept of qualitatively ranking bacterial contamination in the manner described is consistent with the overall risk assessment process outlined. In addition, FDA believes that the incidence of carcass contamination is a relevant factor in estimating the probability of human exposure to foodborne bacteria. For the purposes of this risk assessment, FDA assumes that a high incidence of carcass contamination is more likely to lead to human exposure through food than a low incidence of carcass contamination. Based on this assumption, FDA believes that it is appropriate to rank contamination qualitatively as high, medium, or low.

Food commodity consumption: As an example of food commodity consumption data, *per capita* meat consumption data are provided in Table 2. The data presented are for the year 2001 and are published by the USDA Economic Research Service. FDA recommends that the sponsor reference this type of information when completing the risk assessment for their product. The most recent available information should be used for the assessment. The qualitative rankings provided in Table 2 are illustrative, and represent relative rankings of consumption of the commodities listed for the year 2001.

Table 2: *Per capita* consumption data for red meats, poultry, fish and shellfish for the year 2001.

Commodity	*Per capita* consumption* (pounds per capita per year)	Qualitative ranking**
Beef	62.9	High
Chicken	53.9	High
Pork	46.7	High
Fish and shellfish	15.2	Medium
Turkey	13.7	Medium
Lamb and mutton	0.8	Low
Veal	0.5	Low
Total meat	193.7	

*From USDA Economic Research Service[5]; Boneless, trimmed (edible) weight.

**Qualitative ranking based on relative proportion of the total per capita consumption of meat that is attributable to each of the individual meat commodities.

Food commodity contamination: FDA recommends that the sponsor reference food commodity contamination data when completing the risk assessment for their product. The most recent information should be used for the assessment. The relative qualitative ranking of the level of contamination among various food commodities, High (> 25%), Medium (5–25%), Low (< 5%), is a general ranking, proposed here for illustrative purposes only, and may be subject to modification to more appropriately reflect the most current data.

For illustrative purposes, Tables 3 and 4 present *Salmonella* and *Campylobacter* contamination rates in various animal-derived food commodities.

Table 3. Prevalence of *Salmonella* contamination of various animal-derived food commodities and qualitative contamination rankings.

Commodity	Baseline prevalence (%)[1]	Calendar Year 2001 Prevalence (%)[1,2]	Qualitative ranking[3]
Ground Turkey	49.9	26.2	High
Ground Chicken	44.6	19.5	Medium
Broilers	20.0	11.9	Medium
Market hog	8.7	3.8	Low
Ground Beef	7.5	2.8	Low
Cows/bulls	2.7	2.4	Low
Steer/Heifer	1.0	0.6	Low

[1]As reported in the USDA/FSIS "Progress Report on *Salmonella* Testing of Raw Meat and Poultry Products, 1998-2001"[6]

[2]Prevalence data for CY 2001 for all size slaughter establishments and establishments that produce raw ground product

[3]Relative qualitative ranking of the level of contamination among various food commodities, Low (< 5%), Medium (5 – 25%), High (> 25%), is a general ranking, proposed here for illustrative purposes only, and may be subject to modification to more appropriately reflect the most current data.

Table 4. Prevalence of *Campylobacter* contamination of various animal-derived food commodities and provisional qualitative contamination rankings.

Commodity	Prevalence (%)[1]	Qualitative ranking[2]
Turkeys	90	High
Broilers	88	High
Ground Chicken	60	High
Market hog	32	High
Ground Turkey	25	Medium
Steer/Heifer	4	Low
Cows/bulls	1	Low
Ground Beef	0	Low

[1]Data from national surveys conducted between 1992 – 1997.[7-14]

[2]Relative qualitative ranking of the level of contamination among various food commodities; Low (< 5%), Medium (5–25%), High (> 25%) is a general ranking,

proposed here for illustrative purposes only, and may be subject to modification to more appropriately reflect the most current data.

FDA acknowledges that the calendar year 2001 contamination data listed in Table 3 indicate that all listed food commodities are below their respective *Salmonella* performance standards (i.e., baseline prevalence). For the purposes of the assessment outlined here, FDA has decided to base the criterion for "high" contamination upon the highest level of contamination reported for *Salmonella* in 2001. Therefore, for the year 2001, a prevalence of contamination of greater than 25 percent is considered a "high" level of contamination. The medium and low rankings of contamination are bracketed at 5 to 25 percent and less than 5 percent, respectively. For consistency, as described in Table 4, the same ranking criteria may be applied to other bacteria such as *Campylobacter*. Sponsors may propose alternative criteria and rankings, if data are available to support their position.

3. Summarizing exposure assessment: Ranking human exposure to foodborne bacteria.

Table 5 describes a possible process for estimating the probability of human exposure to the hazardous agent through consumption of animal derived food commodities.

Table 5: Possible process for ranking qualitatively the probability of human exposure to a given bacteria in a given food commodity

	Probability of human exposure to a given bacteria		
	Amount of food commodity being consumed		
Amount of food commodity contamination	**High**	**Medium**	**Low**
High	H	H	M
Medium	H	M	L
Low	M	L	L

4. Exposure assessment conclusion

The outcome of the exposure assessment is intended to estimate the probability that humans will be exposed to the hazardous agent through consumption of animal derived food commodities. FDA recommends that the sponsor use the outcome of the integration process described in Table 5 to reach an overall qualitative rank of a high, medium, or low probability of human exposure to the hazardous agent.

C. Consequence Assessment

FDA believes that the potential human health consequences of exposure to the defined hazardous agent may be qualitatively estimated by considering the human medical importance of the antimicrobial drug in question.

While antimicrobial agents are important for the treatment of infectious disease in humans, certain antimicrobial agents are believed to be of greater importance to the therapy of infectious diseases in humans than are others. Therefore, it is assumed that the human health consequences associated with bacteria that are resistant to drugs of greater importance are more significant than the consequences associated with bacteria that are resistant to drugs of lesser importance.

FDA recommends the sponsor refer to Appendix A of this document to assess the importance of the drug or antimicrobial class in question for human medicine. FDA recommends that the sponsor base the consequence assessment conclusion on the human medical importance ranking and be expressed as critically important, highly important or important. This ranking will be integrated along with the outcomes of the release and exposure assessments to derive an overall risk estimation as described below.

D. Risk estimation:

The risk estimation integrates the results from the release, exposure, and consequence assessments into an overall risk estimation associated with the proposed conditions of use of the drug. FDA recommends that the risk estimation rank drugs as high, medium, or low risk. The risk rankings represent the potential for human health to be adversely impacted by the selection or emergence of antimicrobial resistant food-borne bacteria associated with the use of the drug in food-producing animals.

Table 6 provides a possible method for integrating the outcomes of the release, exposure, and consequence assessments into a single risk estimation ranking. The distribution of risk estimation rankings listed in Table 6 provides an initial indication as to the integration of rankings. Refinement of the risk estimation ranking may be appropriate for specific cases based on available information.

Table 6. Possible risk estimation outcomes based on the integration of the release, exposure, and consequence assessment rankings

Release	Exposure	Consequence	Risk Estimation
low	low	important	low
low	medium	important	low
medium	low	important	low
low	low	highly important	low
low	high	important	medium
high	low	important	medium
medium	medium	important	medium
medium	high	important	medium
high	medium	important	medium
high	high	important	medium
low	medium	highly important	medium
low	high	highly important	medium
medium	medium	highly important	medium
medium	low	highly important	medium
medium	high	highly important	medium
high	low	highly important	medium
high	medium	highly important	medium
low	low	critically important	high
high	high	highly important	high
low	medium	critically important	high
medium	low	critically important	high
low	high	critically important	high
high	low	critically important	high
medium	medium	critically important	high
medium	high	critically important	high
high	medium	critically important	high
high	high	critically important	high

VI. RISK MANAGEMENT CONSIDERATIONS

Possible risk management steps range from denying the approval of a drug application (i.e., the drug is unsafe or not shown to be safe) to approving the application under various use conditions that assure the safe use of the product.

A. Denying approval of a drug application: The Federal Food, Drug, and Cosmetic Act (FFDCA), Sec. 512(d), and regulations promulgated thereunder (see 21 CFR 514.111), provides possible grounds for denying the approval of a new animal drug application. The statutory grounds for denying approval include the results of tests that show the drug is unsafe or the determination that there is insufficient information as to whether the drug is safe. Consequently, denying the approval of an antimicrobial drug application is one possible outcome of an overall safety evaluation which could include the qualitative antimicrobial resistance risk assessment process described above.

B. Drug approval under safe conditions of use: Approval of the use of the drug under those conditions for which safety and effectiveness has been demonstrated is another possible outcome of an overall safety evaluation that could include the qualitative antimicrobial resistance risk assessment process described above.

Drugs considered to be of high concern (with regard to potential human health impact) would typically be associated with more restricted use conditions. Drugs considered to be of lower concern would typically be associated with less restricted use conditions in food-producing animals.

C. The following represent relevant risk management steps or conditions that may be appropriate based on the outcome of the qualitative antimicrobial resistance risk assessment process.

1. Marketing status limitations: Antimicrobial drugs approved for use in animals may be marketed as prescription (Rx), over-the-counter (OTC), or veterinary feed directive (VFD) products. FDA believes that for certain antimicrobial drugs veterinary supervision is critical to assuring the judicious and safe use of the antimicrobial drug. Therefore, such drugs might be approved for limited use by, or under the supervision of, a veterinarian. For other antimicrobial drugs, the requirement for this level of veterinary supervision may not be warranted.

2. Extra-label use prohibition: As provided under 21 CFR 530.21(a)(2), FDA may prohibit the extralabel use of an approved new animal drug or class of drugs in food-producing animals if FDA determines that "the extralabel use of the drug or class of drugs presents a risk to the public health." If significant concerns exist regarding

assurance of drug safety in light of potential extralabel use, extralabel use may be prohibited according to the procedures described in 21 CFR 530.

3. Extent-of-use limitations: FDA believes that "extent of use" is an important factor to consider when determining safe conditions of use for an antimicrobial new animal drug. Table 7 presents a possible process for integration of administration and duration of administration of an antimicrobial drug into a qualitative ranking for "extent of use".

Table 7: Possible process for ranking (High, Medium, Low) of extent of antimicrobial drug use in animals based on duration and method of administration.

Duration of use	Intended administration to:		
	individual animals	select groups or pens of animals	flocks or herds of animals
Short (<6 days)	**L**[1]	**M**[2]	**H**[3]
Medium (6-21 days)	**L**	**M**	**H**
Long (>21 days)	**M**	**H**	**H**

[1]Low, [2]Medium, and [3]High extent of use

In general, administration to groups or pens of animals is defined as administration to a segregated group of animals within a building, house or feedlot, whereas administration to flocks or herds of animals is defined as administration to all animals within a building, house, feedlot. The sponsor may use another definition of these terms that is more reflective of relevant, current animal husbandry practices.

D. The following are examples of additional risk management steps that may be associated with the approval of antimicrobial new animal drugs in food-producing animals.

1. Post-approval monitoring: Antimicrobial new animal drugs intended for use in food-producing animals may be subject to monitoring through a post-approval process, such as the National Antimicrobial Resistance Monitoring System (NARMS).

2. Advisory committee review: When making an approval decision regarding a Category 1 or select Category 2 drugs, FDA may choose to convene an advisory committee to discuss the application.

FDA believes that antimicrobial drugs ranked as **high** risk may be approvable if, after evaluating all supporting information, FDA can conclude that there is a reasonable certainty of no harm to human health when the drug is approved under specific use restrictions. Such a determination would be made on a case-by-case basis and based on a review of the entire application. FDA's concerns associated with drugs estimated to pose high risk may be mitigated through the introduction of risk management steps that minimize resistance emergence or selection associated with any adverse impact on human health.

FDA believes that antimicrobial drugs ranked as **medium** risk may be approvable if, after evaluating all supporting information, FDA can conclude that there is a reasonable certainty of no harm to human health when the drug is approved under specific use restrictions. Interpreting the medium risk category of drugs is more complex than the other categories, since the conclusions for the various risk assessment components are potentially more disparate (i.e., ranging from low to high). However, FDA believes it is appropriate to conclude that drugs in this category are associated with a level of risk that is intermediate between the high and low risk category drugs. Therefore, it is consistent to conclude that a finding of reasonable certainty of no harm might be reached for such drugs when use conditions are intermediately restrictive. Such a determination would be made on a case-by-case basis and based on a review of the entire application.

FDA believes that antimicrobial drugs ranked as **low** risk may be considered approvable if, after evaluating all supporting information, FDA can conclude that there is a reasonable certainty of no harm to human health when the drug is approved under specific use restrictions. Such a determination would be made on a case-by-case basis and based on a review of the entire application. For a drug to be ranked as low risk overall, two of three major components of the risk assessment would have been ranked as low and the third component ranked moderate. FDA believes that a single medium ranking when the other two risk assessment components are ranked low should not substantially increase the overall level of risk. Therefore, combinations involving two low ranks and one medium are consistent with an overall risk estimation ranking of low.

VII. Application of Risk Management Strategies:

The integration process outlined above (Table 6) results in an estimation of the risk that the use of an antimicrobial new animal drug will adversely impact human health. The outcome of the risk estimation (high, medium or low) can be used to help identify steps necessary to manage the risks associated with the proposed conditions of use for an antimicrobial new animal drug.

Examples of risk management steps and how these steps might be applied to manage the estimated level of risk are described below. Table 8 contains three categories (1, 2, and 3) which associate the overall drug risk estimation (i.e., high, medium, or low risk) with a set of possible

risk management strategies. In general, Category 1 includes those drugs ranked "high" in the risk estimation, Category 2 includes those ranked "medium", and Category 3 includes those ranked as "low." However, certain cases may warrant alternative categorization.

Table 8. Examples of potential risk management steps associated with the approval of antimicrobial new animal drugs in food-producing animals based on the level of risk (high, medium, or low).

Approval conditions	Category 1 (High)	Category 2(Medium)	Category 3 (Low)
Marketing Status[1]	Rx	Rx/VFD	Rx/VFD/OTC
Extra-label use (ELU)	ELU Restrictions	Restricted in some cases[3]	ELU permitted
Extent of use[2]	Low	Low, medium	Low, medium, high
Post-approval monitoring (e.g., NARMS)	Yes	Yes	In certain cases
Advisory committee review considered	Yes	In certain cases[3]	No

[1]Prescription (Rx), Veterinary Feed Directive (VFD), Over-the-counter (OTC)
[2]See Table 7 for characterization of extent of use
[3]These risk management steps may be appropriate for certain Category 2 drugs that were ranked critically important for consequence assessment **and** ranked "high" for release **or** exposure assessment

As illustrated in Table 8, drugs in Category 1 are associated with a high risk ranking and would typically be subject to the most restrictive use conditions. Category 3 drugs have the lowest risk ranking and would typically be subject to the least limitations. Category 2 drugs, ranked intermediate for risk to human health, would typically be subject to limitations that are intermediate between those of Categories 1 and 3. Category 2 drugs (as described in Table 8) include several approval conditions that may or may not be applied to all drugs in the category. For example, the table indicates that restrictions limiting extra-label use may be considered for certain Category 2 drugs.

The conditions listed for a given drug category in Table 8 are intended to provide an example of the conditions of use or limitations that FDA might expect to be associated with a drug product in that category. However, FDA's final determination of the approvability of antimicrobial new animal drug applications will depend on a consideration of all information available for the drug application in question. FDA may determine that a proposed drug product can be approved under alternative use conditions/limitations

proposed by the sponsor, if the sponsor provides adequate information to support the safety of the drug under those conditions.

VIII. Summary of Microbial Food Safety Assessment Process

FDA recommends that sponsors choosing to use this process:

- Prepare a hazard characterization (described in pages 7 through 8) and submit the characterization to the FDA for review.
- After review of the hazard characterization, FDA and the sponsor may discuss whether a risk assessment needs to be completed and, if so, what information is recommended for completion of the risk assessment.
- Prepare the risk assessment and submit the assessment to the FDA for review.
- Following review of the safety package as a whole, including the risk assessment, FDA will determine the risk estimation and associated risk management steps applicable to the proposed conditions of use for the antimicrobial new animal drug.

Glossary

Consequence assessment: The consequence assessment describes the relationship between specified exposures to a biological agent (the hazardous agent) and the consequences of those exposures. For the purposes of this risk assessment, FDA has decided that the potential human health consequences of exposure to the defined hazardous agent may be estimated qualitatively by considering the human medical importance of the antimicrobial drug in question.

Exposure assessment: The exposure assessment describes the likelihood of human exposure to the hazardous agent through food-borne exposure pathways. The exposure assessment should estimate qualitatively the probability of this exposure to bacteria of human health concern through food-related pathways.

Hazard: Human illness, caused by an antimicrobial-resistant bacteria, attributable to an animal-derived food commodity, and treated with the human antimicrobial drug of interest.

Hazardous agent: Antimicrobial-resistant food-borne bacteria of human health concern that are in or on a food-producing animal as a consequence of the proposed use of the antimicrobial new animal drug.

Hazard characterization: The process by which one may identify the hazard and the conditions that influence the occurrence of that hazard. This is based upon drug-specific information, bacteria/resistance determinant information, and the methodology for the determination of "resistant" or "susceptible" bacteria.

Release assessment: The release assessment should describe those factors related to the antimicrobial new animal drug and its use in animals that contribute to the emergence of resistant bacteria or resistance determinants (i.e., release of the hazardous agent) in the animal. The release assessment should also estimate qualitatively the probability that release of the hazardous agent would occur. For the purposes of this assessment process, the boundaries of the release assessment span from the point the antimicrobial new animal drug is administered to the food-producing animal, to the point the animal is presented for slaughter or the animal-derived food is collected.

Risk: The probability that human food-borne illness is caused by a specified antimicrobial resistant bacteria, is attributable to a specified animal-derived food commodity, and is treated with the human antimicrobial drug of interest.

Risk estimation: The overall estimate of the risk associated with the proposed use of the drug in the target food-producing animals following the integration of the release assessment, exposure assessment and consequence assessment. The risk rankings represent the relative potential for human health to be adversely impacted by the emergence of antimicrobial resistance associated in a food-borne pathogen with the use of the drug in food-producing animals.

Appendix A

Ranking of antimicrobial drugs according to their importance in human medicine

Objective: This appendix describes a process for ranking antimicrobial drugs with regard to their relative importance in human medicine. FDA recommends this ranking be considered when completing the *hazard identification* and the *consequence assessment* portions of the qualitative risk assessment outlined in this guidance document. The general criteria for determining the importance ranking are outlined and a preliminary listing of various antimicrobial drugs and assigned rankings is provided.

Ranking process: Based on a consideration of the factors described below, specific antimicrobial drugs or classes of antimicrobials should be ranked as to whether they are critically important, highly important, or important to human medical therapy. The assignment of a ranking to a given antimicrobial or class of antimicrobials is dependent upon the degree to which any one or more of the factors described below is applicable to the drug in question. Table A1 provides a ranking based on a consideration of the criteria described below.

The possible importance rankings are defined as follows:

Critically Important: Antimicrobial drugs which meet BOTH criteria 1 and 2 below.

Highly Important: Antimicrobial drugs which meet EITHER criteria 1 or 2 below.

Important: Antimicrobial drugs which meet EITHER criterion 3 and/or 4 and/or 5.

Note: Table A1 does not necessarily include all antimicrobial drugs or drug classes. The development of new antimicrobials for human therapy, the emergence of diseases in humans, or changes in prescribing practices, etc., are among the factors that may cause the rankings to change over time. Therefore, it is the intent of the Agency to reassess the rankings provided in Table A1 periodically to confirm that the ranking is consistent with current circumstances. The rankings of drugs in Appendix A may be subject to change at any time when information becomes available that would impact those rankings. The sponsor may wish to consult with FDA regarding the ranking relevant to their proposed drug at the time the assessment is made.

Criteria considered in ranking process: In developing criteria for ranking antimicrobial drugs with regard to their importance in human medicine, the FDA considered broad issues associated with the efficacy of drugs in human medicine and factors influencing the development of antimicrobial resistance. Specific factors include the usefulness of the drug in food-borne infections, the types of infections treated, the availability of alternative therapies, the uniqueness of the mechanism of action, and the ease with which resistance develops and is transferred between organisms. Note that multiple factors may be applicable to some products, illustrating their considerable importance to human medicine. We recommend that drug sponsors use the

following criteria to rank the importance of drugs in human medicine. The criteria are ranked from most to least important, e.g. criterion 1 is the most important.

1. ***Antimicrobial drugs used to treat enteric pathogens that cause food-borne disease***
   The Infectious Disease Society of America (IDSA) guidelines on the treatment of diarrhea and other sources such as the Sanford Guide provide the drugs typically used in the treatment of food-borne diseases.

2. ***Sole therapy or one of few alternatives to treat serious human disease or drug is essential component among many antimicrobials in treatment of human disease.***
   A. Includes antimicrobials like vancomycin and linezolid for MRSA infections. Although they are not the "sole" therapy, they are one of only a few alternatives.
   B. This would also include a drug like polymyxin where it is one of few alternatives for multi-drug resistant *Pseudomonas aeruginosa* infections.
   C. Rifampin is not only a drug used to treat TB but also it is an essential part of the treatment regimen as the cure rate is lower without it.
   D. Serious diseases are defined as those with high morbidity or mortality without proper treatment regardless of the relationship of animal transmission to humans. For example, rifampin is an essential drug to treat disease caused by *Mycobacterium tuberculosis* (high morbidity and mortality if untreated) even though this is a human pathogen. Gonorrhea occurs only in humans and is not lethal but can result in sterility if left untreated (high morbidity).

3. ***Antimicrobials used to treat enteric pathogens in non-food-borne disease***
   Enteric pathogens may cause disease other than food-borne illness. For instance, *E. coli*, which causes food-borne disease, is also capable of causing diseases as diverse as urinary tract infections and neonatal meningitis.

4. ***No cross-resistance within drug class and absence of linked resistance with other drug classes***
   A. Absence of resistance linked to other antimicrobials makes antimicrobials more valuable. An example is quinolone resistance in pneumococci, which currently does not appear linked to penicillin resistance. On the other hand, penicillin resistance appears to be linked to macrolide, tetracycline, and trimethoprim-sulfamethoxazole resistance in pneumococci.
   B. Cross-resistance within antimicrobial classes and absence of linked resistance may change over time and will need to be updated periodically.
   C. In this context, "cross-resistance" refers to the transmission of resistant determinants between bacterial species or genera and does not refer to transmission of resistant organisms between animals and humans. This is addressed in the release assessment part of the guidance.

5. ***Difficulty in transmitting resistance elements within or across genera and species of organisms***
   A. Antimicrobials to which organisms have chromosomal resistance would be more valuable compared to those antimicrobials whose resistance mechanisms are present on plasmids and transposons.
   B. This does not refer to "ease of transmissibility" from animals to humans of the resistant pathogen as this is addressed elsewhere in the guidance in the release assessment.

Table A1: Potential ranking of antimicrobial drugs/drug classes based on the identified relevant factors. C- Critically important; H- Highly important; I – Important.

	Classification	1) Enteric pathogen responsible for food-born disease	2) Sole/limited therapy or essential therapy for serious disease (See "Comments" for examples)	3) Used to treat enteric pathogens in non-food-borne disease	4) No cross-resistance within class/no linked cross-resistance with other classes	5) Limited risk of transmission of resistance elements within/across species of organisms	Comments
Natural penicillins	H		X				Neurosyphilis: Serious infection due to Group A streptococci
Benzathine pen G							
Penicillin G							
Penicillin V							
Penase Resistant Pens	H		X				Serious infections due to *Staphylococcus aureus*
Cloxacillin							
Dicloxacillin							
Nafcillin							
Oxacillin							
Antipseudomonal Pens	H		X	X			Serious infections due to *Pseudomonas aeruginosa*
Mezlocillin							
Pipercillin							
Pipercillin/tazo							
Ticarcillin							
Ticarcillin/Clav							
Carbenicillin							
Aminopenicillins	H		X	X			Infections due to *Listeria monocytogenes*
Amoxicillin							
Ampicillin							
Ampicillin/Sulbacta							
1st Gen Ceph	I			X			
Cefazolin							
Cafadroxil							
Cephalexin							
Cephradine							
2nd Gen Ceph	I			X			
Cefaclor							
Cefaclor-CD							
Cefamandole							
Cefonacid							
Cefprozil							
Cefuroxime							
Lorcacarbef							

	Classification	1) Enteric pathogen responsible for food-born disease	2) Sole/limited therapy or essential therapy for serious disease (See "Comments" for examples)	3) Used to treat enteric pathogens in non-food-borne disease	4) No cross-resistance within class/no linked cross-resistance with other classes	5) Limited risk of transmission of resistance elements within/across species of organisms	Comments
3rd Gen Ceph	C	X	X	X			Meningitis: Necrotizing enterocolitis
Cefdinir							
Cefixime							
Cefoperazone							
Cefotaxime							
Cefpodoxime							
Ceftazidime							
Ceftibuten							
Ceftizoxme							
Ceftriaxone							
4th Gen Ceph	H		X	X			Sole agent approved for use as empiric monotherapy for neutropenic fever
Cefepime							
Cephamycins	I			X			
Cefotetan							
Cefoxitin							
Carbapenems	H		X	X			Infections due to multidrug resistant gram negative rods
Imipenem							
Meropenem							
Ertapenem							
Monobactams	I			X			
Aztreonam							
Quinolones	I				X	X	
Nalidixic Acid							
Cinoxacin							
Oxolinic Acid							
Pipemidic Acid							
Flouroquinolones	C	X	X	X	X	X	Infections due to multidrug resistant gram negative rods
Norfloxacin							
Ciprofloxacin							
Ofloxacin							
Enoxacin							
Levofloxacin							
Lomefloxacin							
Sparfloxacin							
Grepafloxacin							
Gatifloxacin							
Moxifloxacin							

	Classification	1) Enteric pathogen responsible for food-born disease	2) Sole/limited therapy or essential therapy for serious disease (See "Comments" for examples)	3) Used to treat enteric pathogens in non-food-borne disease	4) No cross-resistance within class/no linked cross-resistance with other classes	5) Limited risk of transmission of resistance elements within/across species of organisms	Comments
Aminoglycosides	H		X	X			
Amikacin							
Gentamicin							Enterococcal endocarditis
Tobramycin							Sole antimicrobial approved for aerosolized therapy in cystic fibrosis
Kanamycin							
Streptomycin							Infections due to *Mycobacterium tuberculosis*
Neomycin							
Netilmicin							
Spectinomycin							Infections due to *Neisseria gonorrhoeae* in pregnancy
Macrolides	C	X	X				Legionnaire's disease: MAC/MAI prophylaxis and therapy
Erythromycin							
Azithromycin							
Clarithromycin							
Clindamycin	H		X				Serious infections due to Group A streptococci: Alternative therapy of infections due to *Staphylococcus aureus* in patients with serious beta lactam allergy
Tetracyclines	H		X				Rickettsial disease: Anthrax therapy/prophylaxis
Tetracycline							
Chlorteracycline							
Demeclocycline							
Doxycycline							
Minocycline							
Glycopeptides	H		X				Infections due to methicillin resistant *Staphylococcus aureus*
Vancomycin							
Streptogramins	H		X				Infections due to vancomycin resistant *Enterococcus faecium*
Dalfopristin/quinupristin							

	Classification	1) Enteric pathogen responsible for food-born disease	2) Sole/limited therapy or essential therapy for serious disease (See "Comments" for examples)	3) Used to treat enteric pathogens in non-food-borne disease	4) No cross-resistance within class/no linked cross-resistance with other classes	5) Limited risk of transmission of resistance elements within/across species of organisms	Comments
Oxazolidones	H		X		X		Infections due to methicillin resistant *Staphylococcus aureus* and vancomycin resistant *Enterococcus*
Linezolid							
Pyrazinamide	H		X				
Isoniazid	H		X				
Rifamycins	H		X				
Rifampin							
Rifabutin							
Chloramphenicol	H	X		X			
Metronidazole	H		X				Infection due to *Clostridium difficile*
Trimeth/Sulfameth	C	X	X	X			Infection due to *Pneumocystis carinii*
Polymyxin B	H		X	X			Infections due to multidrug resistant gram negative rods

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