Annual Report for the Minor Use Animal Drug Program (NECC1702)

FY 2019 – October 1, 2018 to September 30, 2019

**Executive Summary**

* The NECC1702 structure has allowed the current 88 INADAs at the Center of Veterinary Medicine to remain active without payment of maintenance fees.
* A nine-member Coordinating Committee teleconferences on a regular basis to maintain schedules and information on progress and NIFA grant opportunities.
* Coordinating Committee members, Drs. Meg Oeller and Amy Omer of CVM/OMUMS and Dr. Rod Getchell of Cornell University, Northeast Regional Coordinator), attended the *IR-4 Priority Setting Workshop* in September 2019.
* Dr. Rod Getchell has maintained communication with aquaculture and pharmaceutical representatives, as well as fish health stakeholders.
* Dr. Omer completed MUADP’s registration with CVM’s eSubmitter program.
* Progress has been made on nine of 13 current projects.
* A one-year, $200,000 grant application under USDA-NIFA-AFRI-Funding Opportunity Number 007052 entitled, **Therapeutic interventions for disease reduction or treatment** was submitted to assess the efficacy of Florfenicol (AQUAFLOR®), Oxytetracycline (TM200), and Hydrogen peroxide (Perox-Aid®) for parasitic diseases of fish.
* Detailed cost and time estimates of Efficacy, Target Animal Safety and Human Food Safety studies by the National Coordinator concluded direct costs associated with a single abbreviated new animal drug approval (ANADA) would be approximately $700,000 over five years. Various structures are currently under examination to address stakeholder expectations and support.
* Coordinating Committee members have published two-peer review articles and made three presentations of current projects

**NECC1702 Accomplishments and Impacts**

NECC1702 Accomplishments and Impacts are related to the following stated objective and activities described in the 6/26/2017 proposal (in italics):

*1. Provide the formal structure necessary to maintain the 88 INADAs held in the name of the MUADP.*

The NECC1702 structure has allowed the current 88 INADAs to remain active within FDA/CVM without payment of maintenance fees.

*2. Teleconference and meet with NIFA associates to address the development of a tactical science initiative and formation of a unified Regulatory Systems Support Program.*

Under the format of NECC1702, the following Coordinating Committee members (Table 1) teleconferenced on a regular basis to discuss funding opportunities and progress on studies. NIFA assigned liaison, Dr. Mark Mirando provides updates on funding opportunities through the agency.

**Outreach**

Several members of the MUADP Coordinating Committee (Drs. Meg Oeller and Amy Omer of CVM/OMUMS and Dr. Rod Getchell of Cornell University, Northeast Regional Coordinator) attended the *IR-4 Priority Setting Workshop* in September 2019. The members observed the priority-setting activities of IR-4, a program whose mission is essentially identical to that of the Minor Use Animal Drug Program (MUADP) but for plants instead of animals. Attendance at this workshop provided an opportunity for the Committee members to understand the process that IR-4 uses to (1) prioritize the research they conduct, and (2) maintain the involvement of their stakeholders in the prioritization process.

Dr. Rod Getchell has maintained communication with aquaculture and pharmaceutical representatives, as well as fish health stakeholders. Additionally, he works closely with AADAP and other research partners. For example, the progress made on our AQUI-S®20E project was presented at the annual meeting of the Aquaculture Drug Approval Coordination Workshop last July. Additionally, Dr. Getchell updates the NECC1702 Coordinating Committee members on his NECC1702 projects during teleconferences.

**Table 1**. Minor Use Animal Drug Program Coordinating Committee

|  |  |  |
| --- | --- | --- |
| **Name** | **Representing** | **email Address** |
| Amanda Kreuder | Iowa State University | akreuder@iastate.edu |
| Amy Omer | FDA/CVM | [Amy.Omer@fda.hhs.gov](mailto:Amy.Omer@fda.hhs.gov) |
| Cat Bens | Colorado State University | [Cat.Bens@colostate.edu](mailto:Cat.Bens@colostate.edu) |
| John Babish | MUADP/ | [jgb7@cornell.edu](mailto:jgb7@cornell.edu) |
| Margaret Smith | NEAES | [mes25@cornell.edu](mailto:mes25@cornell.edu) |
| Mark Mirando | USDA/NIFA | [mark.mirando@usda.gov](mailto:mark.mirando@usda.gov) |
| Meg Oeller | FDA/CVM | [Margaret.Oeller@fda.hhs.gov](mailto:Margaret.Oeller@fda.hhs.gov) |
| Rodman G. Getchell | Cornell University | [rgg4@cornell.edu](mailto:rgg4@cornell.edu) |
| Ronald Griffith | Iowa State University | [rgriffit@iastate.edu](mailto:rgriffit@iastate.edu) |

**Process Improvement**

Dr. Omer completed MUADP’s registration with CVM’s eSubmitter program. The CVM eSubmitter tool is an electronic, question-based submission tool that allows animal drug sponsors to electronically and securely submit information to CVM. All animal drug sponsors must use eSubmitter to submit information to CVM’s Office of New Animal Evaluation (ONADE).

Having the ability to submit to CVM electronically will provide increased efficiencies in the creation and delivery of submissions to CVM. Additionally, as a registered eSubmitter user, MUADP will now qualify for shortened reactivation or resubmission review times on certain critical submissions, as defined by the latest Animal Drug User Fee Act (ADUFA III).

*3. Continue research on current outstanding projects.*

Thirteen projects are presently active in the Program (Table 2). Details of progress on nine of those this year are provided below.

**Table 2.** Current Projects

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **Formulation** | **Species** | **Indication** |
| Fenbendazole | Premix | Gamebirds | GI Parasites |
| Strontium chloride | Immersion | Salmonids | Otolith Marking |
| Progesterone | CIDR1 | Goats | Estrus synchronization |
| Tulathromycin | Injection | Goats | Respiratory Infection |
| Chlortetracycline | Oral | Lambs | Respiratory Infection |
| Ivermectin | Medical Block | Beef Cattle | *Rhipicephalus microplus* |
| Vaccinal Immunity | Soluble vaccine | Sheep | *Haemonchus contortus* |
| Vaccinal Immunity | Soluble vaccine | Sheep | *Corynebacterium pseudotuberculosis* |
| AQUI-S®20E | Liquid | Striped bass | Sedative |
| AQUI-S®20E | Liquid | Pompano | Sedative |
| Lasalocid | Premix | Pheasants | Coccidiosis |
| Tulathromycin | Injection | Sheep | Respiratory Infection |
| Erythromycin | Premix | Salmonids | Bacterial Kidney Disease |

1. Controlled internal drug release
2. Fenbendazole in quail:

MUADP continues collaboration with our research partners, Dr. Ron Kendall of Texas Tech University and Merck Animal Health, to generate the data necessary to obtain FDA approval of fenbendazole-medicated feed for the treatment of nematodes in quail. This project has impact for both wild quail and farmed quail. Wild quail populations have declined by more than 85% in the last five decades. While many causes for the decline have been proposed, this project addresses the potential role of parasitism. Field studies conducted by Dr. Kendall have shown that fenbendazole is effective against common parasites in quail.

The ongoing research will also support FDA approval for the use of fenbendazole in farmed quail. There are currently no anthelmintics approved for use in quail. Successful completion of this project will provide access to a class of therapeutic drugs previously unavailable to quail farmers.

* 1. Environmental:

MUADP worked with research partner, Merck Animal Health, to justify a claim of categorical exclusion from the requirement to conduct an Environmental Assessment for the use of fenbendazole in quail. The claim was denied by CVM, with a request for additional information. MUADP and Merck are working to address CVM’s requests.

1.2 Human Food Safety:

In April 2019, MUADP, with research partner Dr. Ron Kendall of Texas Tech University, submitted a revised protocol for a tissue residue depletion study for fenbendazole in quail. CVM requested additional revisions to the protocol.

In August 2019, MUADP submitted for CVM review the revised Method SOP and Validation Report. CVM determined that the tissue method for fenbendazole in quail was adequately validated and acceptable for use in a residue depletion study.

* 1. Target Animal Safety and Effectiveness**:**

Dr. Ron Kendall has conducted both a Target Animal Safety study and an Effectiveness study for the use of fenbendazole in quail. The MUADP is preparing these data sets for submission to CVM.

2. Strontium Chloride immersion for salmon:

MUADP continues collaboration with our research partner, Syndel USA, to generate the data necessary to obtain FDA approval of strontium chloride hexahydrate immersion for the skeletal marking of freshwater salmonid fry and fingerlings. Fishery managers need a method to chemically mark salmon to determine migration patterns while avoiding the stress of tagging or other physical markings. While there are other drug products approved for skeletal marking in salmon, this project provides a non-antimicrobial alternative.

* 1. Target Animal Safety:

Dr. Rod Getchell, Northeast Regional Coordinator for the MUADP, completed a GLP Target Animal Safety study evaluating strontium chloride hexahydrate immersion for the skeletal marking of freshwater salmonid fry and fingerlings. In May 2019, CVM determined that the Target Animal Safety technical section was complete for this indication.

1. Efficacy of CIDRs for synchronization of estrus in goats:
   1. No progress to report.
2. Tulathromycin (Draxxin) Tissue Residue in Goats.

4.1 Target Animal Safety: The ultimate objective of this project is to perform studies in support of FDA/CVM approval of a label claim for Draxxin in goats. In the summer and fall of 2017, Dr. Joe Smith conducted work to determine the pharmacokinetics of Draxxin in infected vs uninfected goats (Abstract of presentation at the ACVIM meeting below). In addition, selected target tissues were harvested from the uninfected goats and frozen for determination of tissue residue levels in preparation for conducting a required Human Food Safety study.

4.2 Publication: Preliminary evaluation of a Pasteurella multocida respiratory disease induction model for goats Comparative Medicine (In Press)

5. Efficacy of oral chlortetracycline for control of naturally acquired respiratory disease in feeder lambs.

5.1 Principal investigators: Katelyn Ternus, Dawson LaBorde, Ron Griffith, Paul Plummer, Kelly Still Brooks.

5.2 Objective: The purpose of this study was to evaluate if medicating feeder lambs with oral chlortetracycline (CTC) decreases the prevalence of clinical and subclinical respiratory disease. 5.3 Methods: This study was conducted as a blinded, randomized clinical trial enrolling 160 weaned feeder lambs with natural exposure to ovine respiratory disease. The efficacy of CTC for control of ovine respiratory disease was evaluated through overall average daily gain, ruminal core body temperature, ante mortem clinical respiratory disease scores, post mortem lung lesion scores, and pulmonary tissue culture.

Current project efforts are focused on preparation and laboratory analysis of the banked biologic samples. The ovine plasma CTC concentration determinations have been completed by Scott Wetzlich (UC Davis) and the raw data has been returned to the research team. Dr. Fufa Bari completed DNA library preparation of a subset of the bronchoalveolar lavage samples last fall; viral metagenomic sequencing was run at the ISU VDL and the bioinformatics analysis has been returned to the research team.

These samples will be submitted for tetracycline resistance marker shotgun sequencing at the end of the summer (2018) when the 16s samples are ready for assay. DNA prep for the water biofilm samples is nearly complete and DNA prep of the BAL, fecal, cecal, and rumen samples will be performed this summer, with bulk submission of all samples for 16s sequencing slated for this fall. Coordination is in progress to complete the quantitative feed tetracycline analysis through Zoetis this summer.

1. Ivermectin Molasses/Protein/Mineral Tubs for Eradication of Cattle Fever Ticks.
   1. Report: The study report for this project has been compiled and organized. Plans are to return the report to Dr.Dan Baca for submission to the FDA/CVM. However, the manufacturer has not reached an agreement with Merial for the right of reference and the manufacturer has also not been able to complete the Chemistry and Manufacturing Component. The latter was to be performed before or at least early in the work.
2. Extended Vaccinal Immunity to *Haemonchus contortus* in Sheep.
   1. Principal Investigators: Matt Brewer and Doug Jones.
   2. Methods: 24 sheep were divided into 4 experimental groups: adjuvant only (ADJ), soluble vaccine (SOL), implant with dextran adjuvant (DD), or implant with Quil A adjuvant (DQ). Sheep were infected with 4500 larvae 9 months post-vaccination (12 sheep) or 9000 larvae one year post-vaccination, and necropsied 50-60 days post infection.
   3. Results: Implanted sheep had lower adult worm counts and all vaccinated sheep had decreased egg counts. Vaccination was also associated with a modest increase in PCV. FAMACHA scoring did not reveal any dramatic differences between control and vaccinated animals. Implanted animals had ELISA endpoint titers that were orders of magnitude greater than control animals 55 weeks post-vaccination.  IHC revealed serum antibodies binding to a variety of worm tissues, including the gut and body wall. Statistical analysis, additional IHC, and measurement of cytokines (recall responses) are underway.  We have identified a suitable source of refined *Haemonchus* gut antigen for future experiments. A manuscript describing these results is in preparation.
   4. Figures

Figure 1. Haemonchus contortus vaccine. Adjuvant only (ADJ), soluble vaccine (SOL), implant with dextran adjuvant (DD), or implant with Quil A adjuvant (DQ).



1. Preparation of antigens from three different strains of Corynebacterium pseudotuberculosis
   1. Progress: Study has been completed. Sheep were immunized 3X with each of the antigen preparations and subsequently bled for antibody production. A challenge model in mice has been evaluated at two different dosages and one strain was especially virulent, one strain produced grossly visible lesions but no obvious clinical signs and the third strain produced neither lesions nor clinical signs.
2. Target animal safety study for AQUI-S®20E
   1. Overview: This represents one of our newest NIFA studies.
   2. Methods: A target animal safety study will be conducted for the AQUI-S®20E sedative in striped bass and pompano as model species.

**Estimating Funding Needs for MUADP**

*4. In conjunction with NIFA and stakeholders, identify a stable funding source to work with the FDA/CVM to facilitate their approval of animal health products and provide information for the safe and efficacious use of these materials in specialty animal species.*

To identify a stable funding source, it is necessary to accurately ascertain the current costs of performing Efficacy, Target Animal Safety and Human Food Safety studies under Good Laboratory Practices (21 CFR 58) and Good Clinical Practices. These estimates were performed over the past year using historical costs along with estimates from three commercial histopathology laboratories. All studies were assumed to be conducted under Good Laboratory practices. From required study length, total animal-days were calculated to estimate in life phase costs of each study. Post study estimate of residue analyses was based on one or two edible tissues per species. Gross and histopathology evaluations were based on 38 tissues required by FDA/CVM. Total direct costs thus estimated were $700,000 per species per drug and would require a research period of five years. Adding the costing of the Environmental Impact Assessment and one full time associate, the amount needed per operational unit is approximately $1 MM for the completion of one abbreviated animal drug approval (ANADA) within five years.

Various structures are currently under examination to address stakeholder expectations and support.

**Grant Applications**

Description: USDA-NIFA-AFRI-Funding Opportunity Number 007052 in the animal health program area under “**Therapeutic interventions for disease reduction or treatment.”**

Institution: Researchers within the Cornell University Aquatic Animal Health Program and USFWS Aquatic Animal Drug Approval Partnership (AADAP) program are proposing to continue a collaboration to conduct studies to increase the number of safe and effective drugs that can be used to benefit the U.S. aquaculture community.

Scope of Work: Trials will be conducted with Florfenicol (AQUAFLOR®), Oxytetracycline (TM200), and Hydrogen peroxide (Perox-Aid®), which are used to treat diseases and parasites of fish.

Budget: $200,000 for one year including $60,000 indirect costs

**Presentations and Publications**

Smith, J.S., Mochel, J.P., Seo, Y.J., Ahrens, A.P. and Griffith, R.W. 2020 Preliminary evaluation of a repeated administration *Pasteurella multocida* respiratory disease induction method for goats. Comparative Medicine (In Press)

Yaeger, M. J., Mochel, J. P., Wu, Z., Plummer, P.. Sahin, O., Beyi, A.F., Xu, C., Zhang, Q., and Griffith, R. 2020. Pharmacokinetics of Tulathromycin in Pregnant Ewes Challenged with *Campylobacter jejuni*. Frontiers in Veterinary Science, section Veterinary Pharmacology and Toxicology (Submitted).

Yaeger, M. J., Mochel, J. P., Wu, Z., Plummer, P.. Sahin, O., Beyi, A.F., Xu, C., Zhang, Q., and Griffith, R. 2019 Pharmacokinetics of Tulathromycin in infected vs uninfected goats. ACVIM meeting (Phoenix, AZ)

Getchell, Rodman G., D.M. Scott, B.M. Chambers, N. Wandelear, P.R. Bowser, P. Baneux, D. Kirby, H. Marquis, and M. Blair. 2020. The Safety of AQUI-S® 20E (10% Eugenol) as a sedative on marine fish. Aquaculture America 2020, February 9-12, 2020, Honolulu, HI.

Getchell, Rodman G., Danielle M. Scott, Brian M. Chambers, Niccole Wandelear, Paul R. Bowser, Philippe Baneux, Drew Kirby, Hélène Marquis, and Marilyn Blair. 2019. The safety of AQUI-S® 20E (10% Eugenol) as a sedative on a marine finfish. Aquatic Animal Drug Approval Partnership (AADAP) Program U.S. Fish and Wildlife Service,August 31, 2019 Bozeman, MT