MINUTES
MINOR USE ANIMAL DRUG PROGRAM/NRSP-7 SPRING MEETING 2010
MARCH 25TH AND 26TH, 2010

THURSDAY MARCH 25TH, 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 March 25th and 26th at the FDA Center for Veterinary Medicine (CVM), 7519 Standish Place, Rockville, MD

ATTENDANCE AM MEETING

NAME	AFFILIATION	EMAIL ADDRESS
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The NRSP-7 technical committee is made up of a National Coordinator, four Regional Coordinators, four regional Administrative Advisors, and liaisons from USDA and FDA. The National Coordinator is Dr. John Babish (Cornell University). The Regional Coordinators are Dr. Lisa Tell (University of California, Davis), Dr. Thomas Vickroy (University of Florida), Dr. Ronald Griffith (Iowa State University), and Dr. Paul Bowser (Cornell University). The Administrative Advisors in attendance are Dr. Margaret Smith (Cornell University) and Dr. John Baker (Michigan State University AES), Chairman of Administrative Advisors. The USDA representative is Dr. Gary Sherman (Washington, DC) and the FDA liaison is Dr. Meg Oeller (Rockville, MD).

9:00 – 12:00 INTRODUCTIONS
Introductions and meeting organization

Dr. John G. Babish started the meeting with a round of introductions followed by a description of the program's ongoing efforts to increase funding and dealing with increasing research costs, and more rigorous regulatory requirements that have evolved over the program's twenty-five year existence.

He described the mission of the program as fourfold: *Identify* animal drug needs for minor species and minor uses in major species, *Generate* and *disseminate* data for safe and effective therapeutic applications, and *Facilitate* FDA/CVM approvals for drugs identified as a priority for a minor species or minor use.

To accomplish these goals, the Minor Use Animal Drug Program 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 throughout the country.

Dr. Babish then outlined the format of the meeting as an interaction between CVM reviewers and Regional Coordinators to discuss both general issues as Good Laboratory Practice inspections and specific concerns in recent protocol or research submissions.

Welcome from Dr. Bernadette Dunham

Dr. Dunham, the Director of the FDA Center for Veterinary Medicine (CVM), welcomed everyone and began the discussion with her vision of changes within CVM and the future of the MUMS and MUADP. In her remarks, she again stressed the need for collaboration with stakeholders and the need to demonstrate to the leaders at USDA and in the Congress the impact of the program on both animal health and public health.

Dr. Dunham announced the appointment of Michael R. Taylor as deputy commissioner for foods at the Food and Drug Administration (FDA) in January 2010. He is the first individual to hold the position, which was created along with a new Office of Foods in August 2009. Mr. Taylor is leading FDA efforts to

- Develop and carry out a prevention-based strategy for food safety
- Plan for new food safety legislation and
- Ensure that food labels contain clear and accurate information on nutrition

Dr. Dunham praised the program members for their efforts to ensure funding through continued lobbying and provided guidance into the most effective ways of establishing strong connections with stakeholders and legislators. She provided insight into the budget process both from the standpoint of the agencies of the executive branch and from the congressional side. Changes in the scope of the program and in the funding mechanisms need to be planned well in advance and must be supported by clear objectives and accomplishments. The MUADP/NRSP-7 program has a good story to tell. Dr. Dunham encouraged the members of the program and their stakeholders to take this important message to the USDA and the congress to encourage their support.

She recounted changes at FDA that mirror the need to focus on “One Health” initiatives that link animal and human health concerns. The One Health concept is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans and animals. The synergism achieved will advance health care for the 21st century and beyond by accelerating biomedical research discoveries, enhancing public health efficacy, expeditiously expanding the scientific knowledge base, and improving medical education and clinical care. When properly implemented, it will help protect and save untold millions of lives in our present and future generations.

Finally, Dr. Dunham discussed her plans to make the FDA/CVM web site (http://www.fda.gov/AnimalVeterinary/default.htm) easier to navigate. Among the issues generally cited by visitors to the site, was the desire to follow drugs through the approval process

more accurately. This was contrasted to the ability to follow patent applications through the patent approval process at the US Patent and Trademarks site (http://www.uspto.gov/).

REPORTS FROM THE REGIONS

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 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. This project has been terminated and this termination has been entered into RUSTI. The data from the HFS study has been organized and a technical report written. The final technical report for the human food safety study is undergoing quality assurance review and is projected to be complete by March 31, 2010. Once the QA review is completed, a "road map" for CVM will be created and the technical report submitted.

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. Status of the project needs to be changed.

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* be 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. A draft of the revised environmental assessment report for erythromycin in salmonids is presently in preparation and has a targeted date for completion on December 7th, 2009. The report for the range-finding chronic toxicity study for the *Daphnia magna* has been reviewed and will be submitted to CVM. The EA was sent to Eric Silberhorn on January 20, 2010 for preliminary review. Christine Moffitt is working on the White Paper for submission.

ADR# 311 –Lincomycin soluble powder for foulbrood disease in Honeybees
The human food safety technical section is complete. The effectiveness technical section is pending.

Collaborative Projects:

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.

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.

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 are currently being analyzed from 30 animals. To date, muscle, liver, kidney, and injection site samples have been analyzed from all 30 animals.

Other Projects/Activities:

Excede (Ceftiofur Crystalline Free Acid) 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.

CIDRs for Deer: Conference call with Albert Ramudo. Dr. Ramudo will check into the interest on Pfizer's part for such a study.

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 continue the CIDR-G Efficacy study, finish the analyses for the goat tulathromycin project, and finish the salmonid erythromycin environmental assessment. If the fenbendazole in game bird study starts again, we will be prepared to do the sample analysis.

Manuscripts Submitted, Accepted or Published Since the Last Meeting:

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 that 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.

Northeast Region: Dr. Paul Bowser
Progress of the work and principal accomplishments
The Northeast Region NRSP7 has been without funding from the period of 09/2008 to 09/2009. Due to this financial situation, work accomplished during this period was limited primarily to providing administrative support 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.

Species Grouping Project:
INAD 10-320 Oxytetracycline in Fish
INAD 10-823 Romet-30 in Fish
INAD 11-145 Florfenicol in Fish
No additional work has been performed on this project during this study period.

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 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) in trout, salmon and catfish.

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

Future work is being hampered by a lack of funds in the Northeast Region. We anticipate our efforts on this project to center around the continued provision of administrative support 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.

Other:
We are also considering the development of a project that centers on the question of Iodophore disinfection of fish eggs to prevent the vertical transmission of Viral Hemorrhagic Septicemia Virus. Contact has been made with a potential sponsor,

Western Chemical, which expressed interest in developing collaboration with the MUADP.

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:

To identify animal drug needs for minor species and minor uses in major species,
To generate and disseminate data for safe and effective therapeutic applications, and
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:

(A) Use of hydrogen peroxide for the control of bacterial gill disease in fish.
(B) Species Grouping in Fish, using the compounds Oxytetracycline, Romet-30/Romet-TC and Aquaflor as test articles.

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. Additional work is currently being impacted by a lack of funds in the Northeast Region.

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):

<u>Publications</u>:

Bowser PR, Kosoff RE, Chen C-Y, Wooster GA, Getchell RG, Craig JL, Lim P, Wetzlich SE, Craigmill AL, Tell LA. Florfenicol residues in Nile tilapia after 10-d oral dosing in feed: Effect of fish size. J Aquat Anim Health, 21: 14-17, 2009.

Kosoff RE, Chen C-Y, Wooster GA, Getchell RG, Bowser PR, Clifford A, Craig JL, Lim P, Wetzlich SE, Craigmill AL, Tell LA. Florfenicol residues in three species of fish after 10-day oral dosing in feed. J Aquat Anim Health, 21: 8-13, 2009.
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