MINUTES NRSP-7 FALL MEETING 2006
HOSTED BY US FISH AND WILDLIFE SERVICE
LACROSSE, WI

OCTOBER 10TH AND 11TH, 2006

TUESDAY, OCTOBER 10, 2006

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 10, 2006 at the US Fish and Wildlife Service facilities in La Crosse, WI.

ATTENDANCE

The NRSP-7 technical committee is made up of a National Coordinator, 4 Regional Coordinators, 4 regional Administrative Advisors, and liaisons from USDA and FDA. The National Coordinator is Dr. John Babish (jgb7@conrell.edu Cornell University). The Regional Coordinators are Dr. Arthur Craigmill (alcraigmill@ucdavis.edu University of California, Davis), Dr. Alistair Webb (Webb@ufl.edu University of Florida), Dr. Ronald Griffith (rgriffit@iastate.edu Iowa State University), and Dr. Paul Bowser (prb4@cornell.edu Cornell University). The Administrative Advisors are Dr. Kirklyn Kerr (Kirklyn.Kerr@uconn.edu University of Connecticut), Dr. Garry Adams (gadams@cvm.tamu.edu Texas A&M), Dr. David Thawley (thawley@cabnr.unr.edu University of Nevada), and Dr. John Baker (Baker@anr.msu.edu Michigan State University). The USDA representative is Dr. Gary Sherman (gsherman@CSREES.USDA.GOV Washington, DC) and the FDA liaison is Dr. Meg Oeller (margaret.oeller@fda.hhs.gov Rockville, MD). Dr. Craigmill was unable to attend and was represented by his Regional Coordinator-elect, Dr. Lisa Tell (latell@ucdavis.edu University of California, Davis). Drs. Kerr and Thawley were also unable to attend. This meeting was also attended by the National NADA coordinator for Aquaculture, Rosalie "Roz" Schnick (RozSchnick@centurytel.net). Our host representatives were Drs. William Gingerich and Randy Hines (rkhines@usgs.gov).

TOUR OF THE FACILITIES AND RESEARCH PROGRAMS

Dr. Randy Hines conducted a tour of the facilities that included detailed presentations of all current projects as well as an historical perspective.

PRESENTATION BY NATIONAL NADA COORDINATOR FOR AQUACULTURE

Ms. Roz Schnick gave a presentation, “Aquaculture Drug Approval Highlights of Progress”. She described the achievements of several different entities, including the Upper Midwest Environmental Sciences Center, conducting studies to support drug approvals. Roz reported significant progress on projects exploring claims for Aqui-S™ (anesthetic), chloramine-T, Florfenicol, formalin, hydrogen peroxide, 17 alpha methyltestosterone, and oxytetracycline. She also described a survey that she conducted to identify unmet label claims in the public sector. Results will soon be distributed to the 38 participating states through the Drug Approval Working Group. Ms. Schnick also described her internet-based drug matrix database, which provides general information and reports on the status of studies supporting aquaculture drug development.

FDA'S NRSP-7 LIAISON REPORT

Dr. Oeller reported on CVM current events including an update on MUMS, personnel changes in Office of MUMS, Animal Drug User Fee Act (ADUFA), minor use determinations and CVM commitment to Minor Species. On the status of implementing MUMS regulations, Dr. Oeller indicated that the final designation regulations and the proposed "small numbers" for determining minor use are both pending. The proposed Indexing regulations have been published and the comment period closes 12/20/06. The Office of MUMS has received over 50 Designation requests and has granted 38 of them to date.

With regard to the personnel changes in the Office of MUMS, Dr. Oeller indicated that the transition period for Dr. Bernadette Dunham to take over the position of Dr. Bealieu has begun with completion scheduled for January 2007.

On the Animal Drug User Fee Act (ADUFA), Dr. Oeller indicated that waivers for minor species and minor uses are still available and the ADUFA renewal for NRSP-7 has been granted.

As related by Dr. Oeller, Minor Use Determinations are currently being done on a case-by-case basis and that they are important for ADUFA waivers, Conditional Approval and Designation. The task of Minor Use Determinations will be easier when the "small number" for minor use is officially determined.

In closing, Dr. Oeller emphasized that CVM will (1) continue to support the attempts to get drugs approved for minor species and minor uses, (2) support NRSP-7 through its FDA liaison, (3) provide waiver from ADUFA fees while providing the same quality of service as for those who must pay. Through the Office of Minor Use/Minor Species, CVM will make designations, administer grants, review indexing request, make minor use determinations, and provide outreach to sponsors, industry groups and the public.

REGIONAL COORDINATORS' REPORTS

Northeast Region: Dr. Paul Bowser

Hydrogen Peroxide Project:

ADR 259 Hydrogen Peroxide as a Therapeutic Compound for Bacterial Gill Disease in Fish. (INAD 9493)

No additional work has been performed on this project during this study period.

Species Grouping Project:

INAD 10-320 Oxytetracycline in Fish
INAD 10-823 Romet-30 in Fish
INAD 11-145 Florfenicol in Fish

A primary constraint in the availability of therapeutic compounds for the Aquaculture Community is the relatively large number of fish species that are currently cultured or that have significant potential as commercial species. Currently, research in support of a label for a therapeutic compound must be performed separately for each species for which the label is desired. We have undertaken a project designed to show the similarities in how drugs are handled by different fish species with the goal of supporting a species (crop) grouping concept for fish. We have conducted these studies in a collaborative effort with the Western Region NRSP7. Within this context, to date we have completed the following preliminary Human Food Safety/Tissue Depletion Studies using the following test articles as model compounds:

Oxytetracycline:

1. Walleyes, freshwater fish, 15C and 20C
2. Tilapia, freshwater fish, 25C and 30C
3. Hybrid Striped Bass, saltwater fish, 20C and 25C
4. Summer Flounder, saltwater fish, 17C and 20C
5. Rainbow Trout, cold water trial (8C)

Romet-30:

1. Walleyes, freshwater fish, 20C and 25C
2. Tilapia, freshwater fish, 25C and 30C
3. Hybrid Striped Bass (would not accept the ration;see below)
4. Summer Flounder, saltwater fish, 17C and 20C

Florfenicol (10 mg/Kg/d, 10d):

1. Walleyes, freshwater fish, 20C and 25C
2. Tilapia, freshwater fish, 25C and 30C
3. Hybrid Striped Bass, saltwater, 20C, 25C

Florfenicol (Effect of fish size)

1. Tilapia – 100 gm, freshwater fish,
   25C, 15 mg/Kg, 10d
2. Tilapia – 250 gm, freshwater fish,
   25C, 15 mg/Kg, 10d
3. Tilapia – 500 gm, freshwater fish,
   25C, 15 mg/Kg, 10d

Several attempts were made to conduct human food safety studies or Romet-30 in hybrid striped bass. Although extremely active feeding on a non-medicated ration was observed during acclimation, the hybrid striped bass refused to consume the Romet-medicated ration on all attempts to initiate a trial. As a result, hybrid striped bass were eliminated from our testing matrix for Romet-30. The Sponsor has reported that they have developed a product that circumvents the palatability problem and we anticipate efforts to complete the Human Food Safety/Tissue Elimination studies in that species.

Samples from several of the Florfenicol studies are currently being analyzed in a cooperative effort with the Western Region NRSP7.

USEFULNESS OF THE FINDINGS:

In all cases, the findings 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 (Florfeniol) in trout, salmon and catfish.

WORK PLANNED FOR NEXT YEAR:

ADR 259 Hydrogen Peroxide as a Therapeutic Compound for Bacterial Gill Disease in Fish. (INAD 9493)

No additional work is planned for this project in the upcoming 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 conducting Efficacy Studies, with a focus on oxytetracycline during the coming year. These studies will be performed 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 salmonids and for the 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.

During the coming year we anticipate the completion of tissue assays for samples generated from Human Food Safety/Tissue Elimination Studies of Aquaflor in Hybrid Striped Bass and Tilapia.

Rofenaid in Pheasants INAD 10-804

We are considering the conduct of an efficacy trial of Rofeniad for the treatment of coccidia in pheasants.

Minor Species Efforts in Goats

Preliminary efforts are underway to establish a minor species project in the Northeast Region that will focus on needs of the goat industry. This effort will be under the leadership of Dr. Mary Smith, Department of Clinical Sciences, College of Veterinary Medicine, Cornell University. Specific details of this study are still in the developmental stages.

North Central Region: Dr. Ronald W. Griffith

CIDRg in sheep. Dr. Dennis Hallford at New Mexico State University is completing the assays for determination of progesterone stability in frozen liver and muscle tissue. Interestingly, when fresh liver is spiked with exogenous progesterone, the liver enzyme systems continue to function. Assays for progesterone in liver tissue indicate that only background levels are detected within 1 hour of spiking. The stability assay in frozen liver tissue only needed to be conducted out to 30 days and that portion of the study is completed. Dr. Hallford is continuing to assay for progesterone levels in frozen muscle tissue and will likely complete this in January.

Lasalocid in ring-necked pheasants. A product development conference with ONADE and Alpharma is scheduled for October 18, 2006. A protocol for determination of efficacy has been submitted to CVM. The efficacy studies are being done in cooperation with Dr. Thomas McQuistion in Milliken University in Decatur, Ill. That study should get underway next spring barring any unforeseen developments.

Draxxin in goats and sheep. A product development meeting between the NC Region, ONADE, Meg Oeller and Pfizer was held on October 2, 2006. Protocols for Efficacy, Target Animal Safety, and Human Food Safety (tissue residues) have been submitted to CVM for studies in goats. Once those protocols are reviewed, they will be adapted for sheep. The efficacy study requires significant revision since ONADE is going to require a moderately large field trial.

CIDRg in goats. The assay for progesterone in milk is ready to be validated Dr. Dennis Hallford at New Mexico State University.

Bioclip for shearing sheep. No response from Merial on this project. This product is currently licensed for use in Australia. It is injected subcutaneously into sheep. It causes a wool break and the wool is then shed. A net is placed around the sheep at the same time Bioclip is injected and the net keeps the wool in place. After about a month, the net and fleece are removed. The product works best in Merino or half-Merino sheep.

Regulin for sheep. CEVA is interested but has not decided whether they wish to pursue approval for Regulin in the US. I have protocol approval from ISU's IACUC but have not written any protocols or requested a product development conference. Regulin is a melatonin implant that is approved for use in Australia. It is used to stimulate sheep to come into estrus sooner and has the added benefit of increasing the number of lambs conceived per ewe.

Nuflor in veal calves. No recent activity.

WESTERN REGION: DR. LISA TELL

Progress of Work and Principal Accomplishments:

ACTIVE Regional Projects:

ADR#325 - Florfenicol for sheep for respiratory disease.

Funds expended to date on this project exceed $200,000 of Western Region resources. CVM response regarding submitted MIC data has been received. MIC data accepted for publication in JAVMA.

ADR#324 - Progesterone CIDRs for Goats

The TAS study is complete. Report from the principal investigator is in progress.

ADR#272 - **Romet for Gamebirds**

See species grouping report.

ADR#299 - Pirlimycin for Dairy Goats

No progress since last meeting, move to inactive projects.

ADR#295 - Strontium Chloride for Salmonids. Steve Schroeder

Nothing to report from the region.

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

This project is ready to proceed with the support of Pfizer. Dr. Rowe as indicated interest in being involved with this study.

ADR#135 – Erythromycin in Salmonids

Environmental safety report is in progress. Eric Rosenblum met with Christine Moffit and Meg Oeller. Eric Rosenblum is awaiting reference data for the EA. Once he receives these references he should be close to providing a rough draft version.

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

Collaborative Projects:

ADR#280 - Fenbendazole in game birds (Pheasants, bobwhite quail, partridge)

See Southern Region report.

Species Grouping Fish:

Samples currently undergoing analysis for florfenicol, see Dr. Bowser's report, NER. In our laboratory so far this year, for the fish species grouping project we have analyzed 90 plasma and 335 muscle. WR Laboratory personnel are currently working on the remaining 25 muscle samples from trial 2005-3 and 2005-4 (120 each) and the remainder of the muscle samples from 2004-1 (90).

Other Projects:

Species Grouping:

Krsity Cortright is entering her second year of veterinary school, and has finished her work on the *in vitro* and *in vivo* studies. Her paper on the first portion of the *in vitro* modeling has been accepted for publication in JVPT. Whole animal studies have been run in all species for serum pharmacokinetics of midazolam, the CYP3 marker substrate. Scott Wetzlich has worked out a good method for extracting parent midazolam and metabolites from tissues and has analyzed 1000 liver, muscle, and fat samples. Kristy finished the PBPK modeling this summer using these tissue data to compete her Ph.D. work.

Related and Unfunded Projects:

Nuflor veal calf – Dr. Griffith's samples are complete.

New Projects:

Nothing to report at this time.

SOUTHERN REGION: DR. ALISTAIR I. WEB

PROJECTS IN PROGRESS:

The GLP inspections of our ivermectin assay and in vivo sections by the Western Region has been completed and all issues addressed satisfactorily.

RABBITS

ADR – 107 Ivermectin & Rabbits

The in-vivo human safety has been completed and the tissues are currently being assays. Hopefully that will be completed by the new year and reports prepared for submission to FDA-CVM.

FISH

ADR - 271 Crude Carp Pituitary

The author has not submitted a revised report that could address FDA-CVM's concerns. a rebuttal and we will see if the report is salvageable. What is group's view on funding any repeat on the project given this and low likelihood of a manufacturer being found.

ADR – 235 Ovaprim

UFL Tropical Fish [Roy Yanong] and Syndel are working with CVM to define needs. At present our only involvement is to provide GLP support for any TAS studies. This may be an alternative to CCPE as a spawning aid.

ADR – 236 Metomidate

Following a teleconference with CVM, UFL Tropical Fish [Roy Yanong] has been evaluating behavioral changes as markers of efficacy of metomidate for sedation during transport. Pilot studies have not been promising. This may push them back to studying cortisol depression as a index of stress relief. My anesthesiologist hat is concerned as this group of drugs has a potent depressant effect on adrenal function in mammals which would confound their study.

BIRDS

ADR - 280 Fenbendazole & Gamebirds

The TAS report is nearly complete but lacks investigator's final input and QA . We have received the Western Region's depletion assay results and are preparing a packet for submission to FDA-CVM.

DEER

ADR – 210 Fenbendazole & Red Deer & ADR – 216 Fenbendazole & Fallow

Intervet have indicated that they want us to carry out the human safety part of the approval. We have started negotiations with Dr.Shane Donley on conducting the *in-vivo* work with Western Region but I have made it clear to FDA-CVM that NRSP-7's goal is for "Cervid". In the product conference we were told that studies of WTD, red deer/elk and fallow deer would gain a "Cervid" label.

ADR - 294 Lasalocid And Deer / ADR - 298 Lasalocid And Goats

Problem is that Alpharma will only proceed if there is a zero withdrawal time. We are starting to mount an assay and will carry out initial pilots on two deer and two goats to see if the lasalocid levels are below tolerance.

WORK PLANNED FOR THE REMAINDER OF THE YEAR:

- Maintain lab and staff at GLP level
- Submit early in the new year the all ivermectin for rabbit reports and all fenbendazole reports.
- Organize studies for gaining approval of fenbendazole & lasalocid in deer, and lasalocid in goats.
- Prepare, in coordination with the National Coordinator, INAD submissions for studies conducted under the aegis of the Southern Region. Initial preparation of written responses to CVM review of all of the data submitted for each project. This is often a time consuming and unrecognized activity associated with the completion of each project and may require considerable correspondence and conversation.
- Continued collaborative work with the other regions is anticipated and may include unplanned studies to address critical needs and opportunities to collect data.
- Continue the development of the NRSP-7 web site with full activation of the RUSTi database.

New / Proposed Projects:

Last meeting I reported: Fasinex® in deer continues to interest us but gathers dust while we see how other deer projects go. Trichlorbendazole is a drug that Novartis has approved for sheep, cattle and deer in Europe. It is especially being requested for

red and fallow deer which are unnatural hosts for Fascioloides and it is frequently fatal. Novartis have perked up on this but say their tox package is old and may have a rough passage through FDA. The lure of MUMS and possibility of major species extension later may get them to play. Given problems with deer approvals I would recommend this be put on hold until we have a production line in place.

We have received an ADR for moxidectin in deer from NCSU. Either our invermectin assay or their analytic lab maybe be able to handle the residue assays – Southern region cannot handle this project at this time.

Another possible goat project is flunixin or some other NSAID for relief of pain. Comment re-Southern Region accepting any new projects hold here too.

Web Site

The NRSP-7.org web has continued to function well but is need of some development such as PowerPoint Presentations. The University is cranking-up security and is centralizing control of IT. We are concerned but we have been model citizens plus we actually got our original permission to host the web site without obvious use of the ufl.edu domain from the current head of IT. The MUMSRx web database continues to be updated – it alone receives 1-2 hits each day. Rusti is now fully functional and Laura has returned to full-time work. We will be working with each coordinator to get active projects fully entered into the system.

WEDNESDAY, OCTOBER 11, 2006
The Holiday Inn Express, Onalaska, WI (608-783-6555)

The USDA's Minor Species Animal Drug Program, National Research Support Project #7 (NRSP-7) held its second day of the semi-annual meeting of the technical committee and administrative advisors on October 11th The Holiday Inn Express, Onalaska, WI (608-783-6555)

ATTENDEES

In attendance were the National Coordinator Dr. John Babish (Cornell University), Regional Coordinators Dr. Lisa Tell (University of California, Davis), Dr. Alistair Webb (University of Florida), Dr. Ronald Griffith (Iowa State University), and Dr. Paul Bowser (Cornell University); the Administrative Advisors Dr. Garry Adams (Texas A&M), and Dr. John Baker (Michigan State University); the USDA representative Dr. Gary Sherman (Washington, DC) and the FDA liaison Dr. Meg Oeller (Rockville, MD). Drs. Kerr and Thawley were unable to attend.

8:00 – 9:30

WORKING SESSION

USDA REPRESENTATIVE'S REPORT

Dr. Gary Sherman related that the program's funding is expected to remain at the same level for the foreseeable future. There was also a discussion as to the timing of budget developments and optimizing interactions with our stakeholders and pharmaceutical sponsors.

ADMINISTRATIVE ADVISORS' REPORT

The Administrative Advisors continued the discussion regarding the need for reexamination of the program's mission statement in regard to increased requirements and costs for drug approval without corresponding increases in funding. In this climate, it may be necessary to reconsider the prioritization and number of projects.

The advisors also encouraged continued outreach to stakeholders and pharmaceutical sponsors noting that they can influence congressional support, which the committee cannot. They also continued to encourage development of a strong relationship between NRSP-7 and the Office of MUMS in CVM.

Dr. Adams continued his report emphasizing the necessity of getting more funding, or shifting our priorities. With increasing costs and requirements for getting required studies completed for approval, it is time to reconsider the program goals.

If sufficient money is not available to get approvals, then NRSP-7 needs to focus on getting the data necessary so that the drugs can be used safely in an extra-label manner. The situation with regards to funding is critical. NRSP-7 does not have the funding to offer approvals to FDA/CVM similar to those submitted by industry.

NATIONAL COORDINATOR'S REPORT

Dr. Babish also continued his remarks from the spring meeting that emphasized the need for more outreach to stakeholders to solicit increased funding of the program. He led a discussion about developing inroads to stakeholder lobbing efforts to increasing funding through awareness of the benefits of the program to federal legislators.

SPRING MEETING

The spring meeting is scheduled for Rockville, MD. A discussion concerning the invitees for this meeting concluded with the consensus that NRSP-7 invite both stakeholder groups and pharmaceutical representatives to discuss advancing funding through improvement of lobbing efforts for minor species and minor uses in major species.

Dates considered for the meeting were Feb 26-27, Mar 5-6, and Mar 26-27. It was decided that these dates should be sent to the group for voting and a decision will be made prior to the next teleconference on 11/6/06.

OTHER BUSINESS

There being no other business, the meeting was adjourned.

RESPECTFULLY SUBMITTED:
John G. Babish, Ph.D. Date: 11/3/06
NRSP-7 National Coordinato