Minutes NRSP-7 Fall Meeting 2007
September 27th & 28th, 2007

THURSDAY SEPTEMBER 27TH 2007

LOCATION: Intervet, Inc, Millsboro, DE.

ATTENDEES: From NRSP-7, Drs. John G. Babish, John C. Baker, David G. Thawley, Paul R. Bowser, Ronald W. Griffith, and Alistair I. Webb. FDA/CVM liaison Dr. Meg Oeller and Intervet representatives Drs David Laxton, Carl Johnson and Mr. Brett Whitehead. Also from Intervet in attendance were Drs. Eden Bermingham, Manager, Clinical Development and Celia B. Shelton, Manager, Regulatory Affairs. During the meeting various Intervet personnel attended select portions of the presentations. Dr. Gary Sherman was in attendance via phone conferencing.

NRSP-7 PRESENTATIONS AT INTERVET, INC.

The National Coordinator **Dr. Babish** began the meeting by asking each attendee to give a brief introduction. The introductions were followed by an overview of NRSP-7 by Dr. John G. Babish, who then introduced **Dr. Meg Oeller**. In a brief overviews, Dr. Oeller described the roles of FDA/CVM in the NRSP-7 program. Dr. Oeller also reviewed the recently enacted Minor Use Minor Species legislation. Regional coordinator **Dr. Paul Bowser** presented his work on species grouping in fish. This was followed by presentations by **Drs. Lisa Tell, Alistair I. Webb** and **Ronald Griffith** concerning research activities in their regions and potential for Intervet projects.

INTERVET PRESENTATIONS

Introduction Intervet; Future situation with Schering Plough acquisition: **Carl Johnson**, AM, DVM; Director of Product Development and Regulatory Affairs – Pharmaceuticals

Dr. Johnson described the history, product development processes, current products and future plans of Intervet. He indicated that Intervet has a genuine interest in minor use and minor species drug approvals.

Regulatory and international prospective of MUMS - **David Laxton**, DVM; Regulatory Affairs Manager – Pharmaceuticals

Dr. Laxton presented an overview of Intervet interest in MUMS (Minor Use Minor Species act of 2004) as well as a comparison of U.S. and E.U. approval processes for minor use veterinary drugs.

Technical Service and MUMS issues - **Mr. Brett Whitehead**: Vice President of Equine and Ag Retail

Mr. Whitehead informally restated the strong interest Intervet has in minor use drug approvals.

CONTINUED DISCUSSIONS WITH INTERVET

Following the presentations, discussions between NRSP-7 and Intervet included the current Uses of Intervet products under MUMS, markets needs and sizes for deer, elk, other species and product needs and gaps for MUMS from the Intervet perspective.

Meeting with Intervet concluded at 3:30 pm.

THURSDAY SEPTEMBER 27TH 2007; 4:30 PM

LOCATION: Hampton Inn, 4529 Highway One, Rehoboth Beach, DE 19971
ATTENDEES: Drs. John G. Babish, John C. Baker, David G. Thawley, Paul R. Bowser, Lisa Tell, Ronald W. Griffith, and Alistair I. Webb. FDA/CVM liaison Dr. Meg Oeller

ADMINISTRATIVE REPORTS

REPORT FROM THE ADMINISTRATIVE ADVISORS AND NATIONAL COORDINATOR

A joint meeting of Administrative Advisors and the Technical Committee was held to initiate discussions of the current NRSP-7 funding situation. At the conclusion of this two-hour meeting, it was decided that NRSP-7 should initiate action to move to the competitive special grants section of the USDA/CSRESS budget and rework regional budgets to more accurately reflect the money necessary to perform the efficacy, safety and residue studies in a timely manner. Estimates of $2.5 to $5.0 million per year were discussed.

FRIDAY SEPTEMBER 28TH 2007

LOCATION: Hampton Inn, 4529 Highway One, Rehoboth Beach, DE 19971
ATTENDEES: Drs. John G. Babish, John C. Baker, David G. Thawley, Paul R. Bowser, Lisa Tell, Ronald W. Griffith, and Alistair I. Webb. Dr. Garry Adams attended via teleconferencing. Also present were USDA/CREESS representative Dr. Gary Sherman and FDA/CVM liaison Dr. Meg Oeller. In attendance by teleconference were Drs. Thomas A. Bewick and Monte P. Johnson of USDA/CSRESS.

REPORT FROM USDA/CSREES

Dr. Gary Sherman had arranged for Drs. Report from Thomas A. Bewick and Monte P. Johnson of USDA/CSREES to present on IR-4 structure, activities and methods (teleconference). Following a historical perspective on the growth of the IR-4 pesticide program, there was a general discussion concerning the ways NRSP-7 could take advantage of the IR-4 experiences. It was concluded that, while there are many similarities and differences between the two programs, a strong relationship with stakeholders was essential to the success of IR-4 and would be necessary for growth of NRSP-7. The discussion concluded with suggestions as to how stakeholders could become an active part of the NRSP-7 program and which stakeholders should be brought in immediately.

REPORT FROM FDA/CVM

Dr. Meg Oeller reviewed current activities at CVM for each active project during the regional presentations.

REPORTS FROM THE REGIONAL COORDINATORS

Northeastern Region - **Dr. Paul Bowser**

PROGRESS OF THE WORK AND PRINCIPAL ACCOMPLISHMENTS:

Hydrogen Peroxide Project:

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

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 developed a product (Romet-TC) that circumvents the palatability problem and we anticipate efforts to complete the Human Food Safety/Tissue Elimination studies in that species.

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 (Florfenicol) 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. We also anticipate the completion of Human Food Safety trials with Romet-TC in Hybrid Striped Bass at 20C and 25C.

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 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):

Topic-Popovic, N. J.G. Babish and P.R. Bowser. 2007. Observational study of hepatic cytochrome P-450 protein expression and activity in summer flounder (*Paralichtys dentatus*) following combination ormetoprim-sulfadimetoxine treatment. Chemotherapy 53:313-315.

Kosoff, R.E., C.-Y. Chen, G.A. Wooster, R.G. Getchell, A. Clifford, A.L. Craigmill and P.R. Bowser. 2007. Sulfadimethoxine and Ormetoprim residues in three species of fish after 5-day oral dosing in feed. Journal of Aquatic Animal Health 19:109-115.

Abstracts:

Bowser, P.R., R.E. Kosoff, C.-Y. Chen, G.A. Wooster, R.G. Getchell, A. Clifford, S.E. Wetzlich and A.L. Craigmill. 2007. Florfenicol residues in three species of fish after 10-day oral dosing in the feed. Annual Meeting of the Fish Health Section of the American Fisheries Society. Jackson Hole, WY. 5-7 June 2007.

Bowser, P.R., R. E. Kosoff, C.-Y. Chen, G. A. Wooster, R. G. Getchell, A. Clifford, S.E. Wetzlich and A. L. Craigmill. 2007. Florfenicol Uptake and Depletion in Tilapia (*Oreochromis niloticus*) of Various Sizes. 32nd Eastern Fish Health Workshop. Gettysburg, PA. 19-22 June 2007.

Southern Region – **Dr. Alistair I. Web**

PROGRESS OF WORK AND PRINCIPAL ACCOMPLISHMENTS

RABBITS

ADR – 107 Ivermectin & Rabbits

The in-vivo human safety has been completed, assay validated. Analyses of the incurred samples will be completed by winter and reports prepared for submission to FDA-CVM. This is being treated as secondary to the fenbendazole in gamebirds.

FISH

ADR - 271 Crude Carp Pituitary

The author has submitted a revised report that might address FDA-CVM's concerns.

ADR – 235 Ovaprim

UFL Tropical Fish [Roy Yanong] and Syndel are working towards indexing. Close project.

ADR – 236 Metomidate

UFL Tropical Fish [Roy Yanong] and Syndel are working towards indexing. Close project.

BIRDS

ADR - 280 Fenbendazole & Gamebirds

The TAS report continues to be incomplete but lacks investigator's final input and QA we are planning a 90 day completion. The human safety report has been completed and sent to UC-Davis & Intervet for QA. If critics are happy, this will be submitted to FDA within 45 days.

DEER

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

Intervet has indicated that they want to carry out a dose study before moving on this project. This is with Don David at TAMU.

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 well into validating an assay and will carry out initial pilots on two deer and two goats to see if the lasalocid levels are below tolerance. See below for TAMU collaboration.

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 collaborative 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 possible re-implementation of the RUSTi database.

New / Proposed Projects:

With no assured funding in sight, no new projects are under consideration with primary effort being made to complete existing studies and perhaps try a collaboration with TAMU.

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 stalled with loss of biological scientist and concern about bringing on new folk.

Western – **Dr. Lisa Tell**

PROGRESS OF WORK AND PRINCIPAL ACCOMPLISHMENTS

ACTIVE Regional Projects:

ADR#325 - Florfenicol for sheep for respiratory disease.

We are waiting to see what the manufacturer status of this product will be.

ADR#324 - Progesterone CIDRs for Goats

TAS report has been submitted. Milk residue study is in progress (started 9/15/07). Efficacy protocol has been written and will be submitted.

ADR#272 - **Romet for Gamebirds**

See species grouping report.

ADR#299 - Pirlimycin for Dairy Goats

No activity on this project at this time.

ADR#295 - Strontium Chloride for Salmonids. Steve Schroeder

There is nothing to report. Status of the project might need 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

We are waiting for the response from CVM regarding the Environmental Assessment Report.

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

We are waiting for the data to be summarized.

Collaborative Projects:

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

See Southern Region Report.

QA of the Human Food Safety and Target Animal Safety Reports to be done by Ms. Sandra Ogletree.

Species Grouping Fish:

See North Eastern Region Report.

Samples analysis for florfenicol is complete. For the fish species grouping project we have analyzed 240 muscle samples this year from trials 2005-4 (120 samples) and 2004-1 (120 samples).

ADR#324 – Progesterone CIDRs for Goats: Milk Residue Study

See North Central Region Report.

QA of Milk Residue CIDR-G Protocol has been completed by Ms. Sandra Ogletree.

ADR#340 - Tulathromycin in Goats

See North Central Region Report.

QA review of TAS protocol is to be done by Ms. Sandra Ogletree.

The LCMS should be operational by the middle to later part of October. At that time, the Western region will start working on establishing the approved method in our laboratory.

Other Projects:

Avian Species Grouping

Krsity Cortright has finished her work on the *in vitro* and *in vivo* studies. She is completing her work for her PhD.

Excede in Goats:

In collaboration with Drs. Rowe and Angelos, Dr. Elizabeth Dore (UC Davis 3rd year Food Animal Resident) is doing a study evaluating use of Excede in both lactating and non-lactating goats. This study was initiated in September of 2007 in the non-lactating goats and will be completed in June of 2008 in the lactating goats.

New Projects:

Nothing to report at this time.

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 Next Year:

The completion of the Milk Residue CIDR-G project and CVM review of the CIDR-G Efficacy Protocol is the primary project work planned for next year. We will also work to have the approved tulathromycin method established on the LCMS and begin analyzing samples for Dr. Griffith. Species grouping work for fish will continue, as we will be evaluating the fish romet samples.

Publications issued or manuscripts approved since the last meeting:

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.

North Central – **Dr. Ronald W. Griffith**

PROGRESS OF THE WORK AND PRINCIPAL ACCOMPLISHMENTS

Sheep CIDR-g Tissue Residue Stability

This study is being performed by Dr. Dennis Hallford at New Mexico State University in cooperation with both the Western and North Central Regions. The assays for the freezer stability of progesterone have been completed, the data has been submitted to the CVM for review and apparently there is a problem that will prevent this study from being accepted. We have yet to receive notification of the nature of the problem. Depending on the problem, we may need to re-do all or part of the study.

Goat CIDR-g Tissue and Milk Residue

The milk residue assay has been validated by Dr. Hallford and the study is underway at UC-Davis. Phase 1 of the sample collection should be complete within two weeks and sampling of progesterone levels in milk of pregnant goats will be performed at approximately 50 days of gestation.

The tissue residue studies in goats will probably be delayed until we find out what is wrong with the sheep data. It is likely that the goat tissue residue work will not be done until 2008.

Draxxin Efficacy in Goats

The protocol for a natural exposure model has been accepted by CVM. However, the studies are predicted to take at least three years to complete and will require a significant portion of the financial resources of the NC Region. An alternative protocol based upon determination of AUC/MIC is being prepared.

Draxxin Target Animal Safety

The protocol has been reviewed by CVM. Changes were made to reflect the comments from the reviewers. The protocol has been sent to Scott Wetzlich at UC-Davis for review and the addition of a residue analysis protocol.

Draxxin Tissue Residue

The protocol has been reviewed by CVM and there were relatively few comments. The protocol was amended and sent to Scott Wetzlich for review. The method for tissue extraction and tulathromycin analysis is currently being developed.

Lasalocid Efficacy in Pheasants

The study protocol was accepted by CVM and the work was performed by Drs. Larry McDougald and Lorraine Fuller at the University of Georgia with the assistance of Dr. Thomas McQuistion from Milliken University. Dr. Fuller is still analyzing the data and preparing a report.

Regulin (melatonin) implants for sheep

No activity to report.

SPRING MEETING

It was decided that the spring meeting should be organized to take advantage of the lobbying efforts of the NRSP-7 stakeholders, which occurs in the first quarter of the calendar year. Over the next two months specific stakeholders will be contacted for their availability and scheduling of the spring meeting or teleconferences will be completed.

OTHER BUSINESS

There being no other business, the meeting was adjourned at 1:00 pm

Respectfully submitted:

John G. Babish, Ph.D. Date: 10/30/07
NRSP-7 National Coordinator