

Second Mid-Year Report of Progress

Performance Period: July 1, 1995 to December 31, 1995

Approval of Drugs for Public Fish Production

A project of the

International Association of Fish and Wildlife Agencies (IAFWA)

by

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INTRODUCTION

A partnership was developed between the National Biological Service (NBS), the U.S. Fish and Wildlife Service (FWS), and the International Association of Fish and Wildlife Agencies (IAFWA) on behalf of state fish and wildlife agencies to conduct research for the approval of aquaculture drugs by the U.S. Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM).

Research to gain New Animal Drug Application (NADA) approvals or extensions of approvals for eight drugs identified as high priority by the states and to establish crop grouping was initiated July 1, 1994 and will extend until June 30, 1999. During that 5-year period, 37 states will contribute nearly \$3.5 million, NBS's Upper Mississippi Science Center (UMSC, formerly National Fisheries Research Center, La Crosse, Wisconsin) will provide \$4.0 million, and the Fish

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Farming Experimental Laboratory, Stuttgart, Arkansas (FFEL) will provide some base funding toward: a) development of data under good laboratory practices (GLP) provisions to gain CVM approval of NADAs for use in aquaculture for the following essential drugs; 1) extension of formalin to other species, 2) expansion to other diseases and extension to other species for oxytetracycline, 3) copper sulfate, 4) chloramine-T, 5) sarafloxacin hydrochloride (sarafloxacin), 6) potassium permanganate, 7) benzocaine, and 8) hydrogen peroxide; and b) development of research data to support the acceptance of a crop grouping concept by CVM. Data will be generated and CVM will assess whether a few selected fish species can be used as surrogates for all or most of the cultured fishes in the United States.

The development of aquaculture NADAs through the IAFWA project is contingent upon continued base funding at UMSC of \$867,000 per year (reduction of \$100,000 in FY 1996) designated for chemical and drug registration activities, contribution of some base funding from FFEL, and state funding of at least \$740,000 per year under a five-year agreement through the IAFWA. A portion of the states contribution (\$50,000 to \$140,000 per year) and FFEL base funding will be used by FFEL for research on copper sulfate and potassium permanganate. The remainder of the state funding (\$620,000 to \$635,000 per year) and UMSC base funding will be used directly by UMSC to conduct internal studies or to contract for external studies to achieve original or extended NADAs. The proposed studies to be conducted by UMSC and FFEL are estimated to cost \$8.9 million and only \$7.5 million is available, resulting in a need for an additional \$1.4 million.

**HIGHLIGHTS OF PROGRESS:
(July 1, 1995 to December 31, 1995)**

- **Benzocaine:** A final report describing the effects of temperature on the loss of benzocaine and its major metabolite, acetyl-benzocaine, from channel catfish fillet tissue was submitted to the Office of Science, CVM, FDA. The study provides the agency with important information on the nature of the loss of benzocaine from treated fish and the relative composition of the metabolites in the edible portion of the fish with time after exposure.
- **Chloramine-T:** CVM accepted the data in two studies as satisfying requirements for total residue depletion and metabolism of chloramine-T in rainbow trout. They concluded from the data that para-toluene sulfonamide is the major metabolite that results from chloramine-T exposure in fish. This information will allow the agency to declare para-toluene sulfonamide as a marker residue for chloramine-T in juvenile rainbow trout.
- **Copper Sulfate:** A study was completed to determine the accumulation of copper in channel catfish exposed to copper sulfate. This data indicates that copper does not accumulate in fish tissue and will be used to fulfill the residue chemistry portion of the human food safety data requirements for a NADA for copper sulfate.
- **Crop Grouping:** A second research work order was developed and initiated with Dr. William L. Hayton, College of Pharmacy and Pharmaceutical Sciences, The Ohio State University, to undertake the benzocaine portion of the Crop Grouping study plan.
- **Formalin:** A Target Animal Safety Study on the toxicity of formalin to warm- and coolwater fish eggs was completed and the final report submitted to CVM along with a sample formalin label on December 15, 1995. This data will support the extension of the current formalin label as a fungicide to include the eggs of warmwater and other coolwater species.
- **Formalin:** A compassionate Investigational New Animal Drug (INAD) exemption was renewed to allow extended use and efficacy evaluation of formalin as a fungicide at public aquaculture facilities. The study protocol was revised 11/95 and approval for a second year of study was obtained from CVM. Efficacy data generated will be used to support extension of the current formalin label to include fish and the eggs of warmwater and other coolwater species.
- **Hydrogen Peroxide:** A target animal safety study on the toxicity of hydrogen peroxide to representative warm- and coolwater fish eggs has been completed. A report will be submitted soon to CVM requesting an amendment to the current low regulatory priority ruling on hydrogen peroxide to allow its use at concentrations up to 1,000 L/L (ppm) on fish eggs.
- **Hydrogen Peroxide:** Efficacy studies continued in order to delineate the efficacy of hydrogen peroxide for controlling fungal infections on salmonid eggs and to develop a standard method for inducing fungal infections on fish for use in efficacy studies.

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Negotiations and Contract Coordination: Two major INAD\NADA coordination meetings were held. The first was held in Bozeman, Montana on August 1-4, 1995, and the second in Rockville, Maryland on November 1-2, 1995. These meetings resulted in increased communications, more coordination, and some consolidation of INADs.

- **Potassium Permanganate:** A research protocol entitled " Accumulation of Manganese in Edible Muscle of Channel Catfish (*Ictalurus punctatus*) Following Exposure to Water Borne Potassium Permanganate" was approved by the FDA's National Center for Toxicology Research (NCTR) and CVM on September 17, 1995. The study was initiated January 23, 1996.

SUMMARY OF PROGRESS BY RESEARCH STUDY PLAN

A summary follows on the progress made during the period from June 30, 1995 to December 31, 1995 for each of the ten Research Study Plans in the IAFWA Project.

STUDY NO. 1: EXTENSION OF FORMALIN LABEL FOR USE AS A FUNGICIDE ON FISH AND THEIR EGGS PRODUCED AT PUBLIC AQUACULTURE FACILITIES.

Objectives: To develop suitable efficacy and target animal safety data to extend the current New Animal Drug Application (NADA) for formalin to include its use to control fungal infections on eggs and adults of publicly cultured freshwater fish.

Job No. 1: Supervision of the formalin compassionate Investigational New Animal Drug (INAD) permit.

Progress: UMSC staff continued to supervise the progress of the formalin compassionate INAD. The study protocol for the FWS's formalin INAD was revised in November of 1995 and approved for use by CVM for another year. In August of 1995 an INAD implementation and coordination meeting in Bozeman, Montana was attended by the FWS's INAD coordinators, study monitors and UMSC NADA coordinators. Formalin treatments have been administered under the INAD and data from the first year have been gathered and discussed. Efforts continue to identify hatcheries to provide high quality pivotal data for the new NADA. The UMSC has continued to contact INAD holders and discuss the eventual collection, pooling, and analysis of all data to support the new NADA.

Current Status: The formalin (fungicide) INAD has been revised and implemented for a second year. CVM is currently reviewing a data package on formalin that could result in a label extension to include fungicide use on fish and eggs of warmwater and other coolwater fish in 1996.

Job No. 2: Conduct controlled laboratory studies on a variety of fish species to evaluate the efficacy of formalin as a fungicide on cultured freshwater fish and their eggs.

Progress: Efficacy studies of formalin treatments on fish eggs have been completed and no further research is planned pending CVM's decision on extension of the formalin label to include other species not listed on the current label.

The UMSC has revised a protocol and initiated a second study to induce fungal infections on adult fish. If the UMSC is successful in inducing fungal infections on adult fish, the efficacy of formalin as a fungicide on fish will be evaluated. Preliminary studies to induce fungal infections on channel catfish and administer formalin treatments have been conducted.

Current Status: A draft protocol for inducing fungal infections on adult fish has been completed and studies will begin in March 1996. Efficacy research on fish eggs has been completed and no further egg studies are planned at this time.

Job No. 3: Conduct target animal safety studies on adult fish and fish eggs with formalin in support of its extended use as an antifungal agent in public aquaculture.

Progress: Research has been completed to evaluate the safety of formalin treatments on the eggs of five species of fish. The final report entitled "Safety of Formalin Treatments on Fish Eggs" was submitted on December 15, 1995 to CVM in support of the extension of the formalin NADA to include the eggs of additional warm- and coolwater fish species not currently on the product label.

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Current Status: The final report on the Formalin Target Animal Safety Study is currently being evaluated by CVM to support extension of the label to other species of fish.

STUDY NO. 2: EXPANSION OF OXYTETRACYCLINE FEED ADDITIVE FOR CONTROL OF BACTERIAL DISEASES AND OTOLITH MARKING ON FISH.

Objectives: To extend the feed additive label for treatment of certain bacterial diseases on cool- and warmwater fish species of importance to public fish production and to cover marking of fish species not covered by the current label. To expand the feed additive label for control of flexibacteriosis on cold-, cool-, and warmwater fishes.

Job No. 1: Develop efficacy data or determine if current data is adequate on oxytetracycline to expand the label.

Progress: UMSC personnel discussed coordination of data acquisition from INADs for oxytetracycline with FWS and the Western Regional INAD Project.

Current status: Efforts will be required to determine the success of oxytetracycline use in the INADs. Some of the INAD treatments are at higher dosages and for longer durations than the approved uses. This will be an important consideration for other required studies, especially for the residue depletion studies.

Job No. 2: Develop residue chemistry data on oxytetracycline in cool- and warmwater fish.

Progress: Work on an analytical method for oxytetracycline in edible fish tissue is under way to determine accuracy and precision of the method for several species of fish (cold-, cool-, and warmwater). CVM is requiring a bridging study between the official microbiological method and a HPLC method. A similar type of study was completed by FDA laboratories in Seattle and Denver for shrimp tissue. An additional bridging study with fish tissue was planned by the FDA laboratories; however, key personnel have either left FDA or are retiring. UMSC obtained documents for the bridging study for shrimp from FDA and are planning to conduct and coordinate the bridging study for fish tissue.

Current status: Development of information on an HPLC method for oxytetracycline in fish will continue. A protocol will be developed to conduct a bridging study for the microbiological and HPLC method.

Job No. 3: Develop target animal safety data on oxytetracycline in cool- and warmwater fish.

Progress: No activity during July 1, 1995 to December 31, 1995.

Current Status: Testing will begin with the development of efficacy data and when other jobs are completed.

STUDY NO. 3: APPROVAL OF COPPER SULFATE TO CONTROL EXTERNAL PROTOZOAN AND METAZOAN PARASITES AND BACTERIAL AND FUNGAL DISEASES OF CULTURED FOOD FISH.

Objectives: To gain approval of copper sulfate as a therapeutant to control external protozoan and metazoan parasites, bacterial, and fungal diseases of cultured food fish.

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Job No. 1: Develop research protocols for determining distribution of residual copper in organs and tissues of fish that have been exposed to copper sulfate.

Progress: Job No. 1 was completed September 30, 1994. A research protocol entitled "Accumulation of Copper in Edible Muscle of Channel Catfish (*Ictalurus punctatus*) Following Exposure to Water Borne Copper Sulfate", was approved by both NCTR and CVM September 30, 1994.

Current Status: Job No. 1 completed.

Job No. 2: Conduct studies of residues of copper in organs and tissues of cultured channel catfish that have been exposed to copper sulfate at therapeutic levels.

Progress: Laboratory work for this study has been completed. Tissue residue analysis data were examined for conformity with the guidelines for error acceptability and nonconforming sample analyses were rejected. Rejected samples were reprocessed and residue analyses repeated. All sample analyses are now complete and the compilations, calculations, and evaluation needed to prepare the report for NCTR and CVM are underway. It is concluded from this study that exposure of channel catfish to high concentrations of water borne copper sulfate does not elevate residual copper in edible flesh.

Current Status: The final report of the study is expected to be completed and submitted to NCTR by March 1, 1996.

Job No. 3: Prepare an environmental assessment of the fate and effects of release of copper sulfate treated water.

Progress: An assessment of the fate and effects of release of copper sulfate treated water has been completed and is now undergoing revision to meet CVM organizational guidelines.

Current Status: Environmental assessment is being revised to meet CVM requirements.

Job No. 4: Conduct studies of residues of copper in organs and tissues of cultured food fish other than channel catfish that have been exposed to copper sulfate at therapeutic levels.

Progress and Current Status: No activity during July 1, 1995 to December 31, 1995.

STUDY NUMBER 4: APPROVAL OF CHLORAMINE-T TO CONTROL BACTERIAL GILL DISEASE ON SALMONIDS AND FLEXIBACTERIOSIS ON COLD-, COOL-, AND WARMWATER FISH SPECIES

Objectives: To develop data on mutagenicity, environmental fate, residue chemistry, efficacy, and target animal safety that satisfy CVM requirements to support the approval of chloramine-T to control bacterial gill disease (BGD) and flexibacteriosis on cultured freshwater fish.

Job No. 1: Conduct a mutagenicity study in support of the approval of Chloramine-T as a drug.

Progress: No activity during July 1, 1995 to December 31, 1995.

Current Status: CVM must review mammalian toxicology data for chloramine-T before a decision is made whether a mutagenicity study is required for the drug approval submission. The information to be reviewed will be supplied by the pharmaceutical sponsors. To date, potential sponsors have not supplied toxicity data to CVM for review.

Job No. 2: Environmental fate and effect studies in support of the approval of chloramine-T as a drug.

Progress: No activity during July 1, 1995 to December 31, 1995.

Current Status: CVM must review environmental fate and effect data for chloramine-T before a decision is made whether environmental studies are required for the drug approval submission. Potential pharmaceutical sponsors may be able to supply much of the environmental fate information.

Job No. 3: Supervision, data collection, and analysis of efficacy data collected from the FWS compassionate INAD for use of chloramine-T at FWS hatcheries.

Progress: The first year of FWS's INAD for use of chloramine-T for treatment of BGD and flexibacteriosis on fish raised at public aquaculture facilities was completed. Data collected during the first year was reviewed and used to revise the INAD protocol for a second year of use. As part of the INAD process, two meetings of the INAD coordinators were held during this reporting period. The first FWS coordinators meeting was convened at Bozeman, Montana on August 1-4, 1995. There was also an INAD Coordinators Workshop held at Rockville, Maryland on November 1-2, 1995. Personnel from CVM attended this meeting and explained how to use the information gathered from the INAD process to support eventual NADA submissions.

Current Status: The protocol for the chloramine-T INAD was revised to accommodate more effective treatment regimes and to include provisions for prophylactic treatments. There are currently 52 hatcheries involved in collecting efficacy data through the INAD process to support the eventual NADA for chloramine-T.

Job No. 4: Residue chemistry studies to support the approval of chloramine-T as a drug.

Progress: CVM notified UMSC that two studies submitted to support the total residue depletion studies for chloramine-T in exposed rainbow trout were adequate for them to calculate a tolerance for chloramine-T in juvenile rainbow trout. Furthermore, CVM concluded that the major metabolite that results from chloramine-T treatment is para-toluene sulfonamide.

Current Status: With the rulings above, UMSC can begin to develop a regulatory method for the marker residue of chloramine-T by exposure of rainbow trout to para-toluene sulfonamide. Once

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a residue method has been developed, the method will be validated in several analytical research laboratories and the results submitted to CVM for review.

Job 5: Target Animal Safety Studies in Freshwater Fish to Support the Approval of Chloramine-T as a Drug.

Progress: No activity during July 1, 1995 to December 31, 1995.

Current Status: Target animal safety studies are scheduled to be initiated during the second half of FY-1996. Initial protocols are currently in preparation.

STUDY NUMBER 5: APPROVAL OF SARAFLOXACIN HYDROCHLORIDE AS A DRUG TO CONTROL FLEXIBACTERIOSIS AND FURUNCULOSIS IN FRESHWATER FISH

Objectives: To develop efficacy, target animal safety, and total residue and metabolism data required for the use of sarafloxacin in the control of furunculosis and flexibacteriosis in freshwater cold-, cool, and warmwater fish.

Progress: This project has been given low priority since FDA has decided to severely restrict the use of all fluoroquinolones as animal medicinal drugs.

Current Status: No change in status since the report in the first annual report of progress issued in September 1995.

STUDY NO. 6: APPROVAL OF POTASSIUM PERMANGANATE TO CONTROL EXTERNAL PROTOZOA AND METAZOAN PARASITES AND BACTERIAL AND FUNGAL DISEASES OF CULTURED FOOD FISH.

Objectives: To gain approval of potassium permanganate as a therapeutant to control external protozoan and metazoan parasites and bacterial and fungal diseases of cultured food fish.

Job No. 1: Develop research protocols for determining distribution of residual manganese in organs and tissues of fish exposed to potassium permanganate.

Progress: A research protocol entitled "Accumulation of Manganese in Edible Muscle of Channel Catfish (*Ictalurus punctatus*) Following Exposure to Water Borne Potassium Permanganate", was prepared and submitted to NCTR and CVM for review. The protocol was approved by NCTR and CVM on September 17, 1995.

Current Status: The Study will be initiated January 23, 1996.

Job No. 2: Conduct studies of manganese residues in organs and tissues of cultured channel catfish exposed to potassium permanganate at therapeutic levels.

Progress: All preparation and preliminary work has been completed and the study is in progress.

Current Status: The residue study on manganese is in progress.

Job No. 3: Prepare an environmental assessment of the fate and effects of release of potassium permanganate treated water.

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Progress and Current Status: A preliminary search for literature has been completed, a reference file containing 400 entries has been compiled, and a review of this material continues to proceed.

Job No. 4: Conduct studies of manganese residues in organs and tissues of cultured food fish other than channel catfish exposed to potassium permanganate at therapeutic levels.

Progress and Current Status: No activity during July 1, 1995 to December 31, 1995.

STUDY NUMBER 7: APPROVAL OF BENZOCAINE AS AN ANESTHETIC AND SEDATIVE FOR FISH

Objectives: To develop efficacy, target animal safety, and residue depletion data required for the approval of benzocaine as an anesthetic/sedative with a short withdrawal time for several species of freshwater fish.

Job No. 1: Development of a compassionate INAD request to evaluate benzocaine as an anesthetic/sedative for fish cultured on public hatcheries.

Progress: No activity during July 1, 1995 to December 31, 1995.

Current Status: Lack of progress in this job is due to the lack of a pharmaceutical sponsor for benzocaine. A compassionate INAD will not be initiated until a sponsor is identified who can proceed with a NADA.

Job No. 2: Residue chemistry studies in freshwater fish to support the use of benzocaine as an anesthetic/sedative.

Progress: The final report from the study to define the effects of temperature on the loss of benzocaine and acetylated benzocaine in channel catfish (Interagency Agreement Number 224-92-7036) was submitted to the CVM's Office of Science, on October 5, 1995. Methods to extract, separate, and quantify benzocaine and its principle metabolite, acetylated benzocaine in rainbow trout were completed and a companion study to the channel catfish study above was conducted. Fillet tissues of rainbow trout exposed to benzocaine at two temperatures were analyzed for benzocaine and acetylated benzocaine residues.

Current Status: The study to define the effects of temperature on the loss of benzocaine and acetylated benzocaine in channel catfish is complete. The analytical work for the companion study with rainbow trout is complete. The final report for the study with rainbow trout is in preparation.

Job No. 3: Target animal safety studies in rainbow trout and a second species (cool- or warmwater) to support the approval of benzocaine as an anesthetic/sedative.

Progress: No activity during July 1, 1995 to December 31, 1995

Current Status: Target animal safety studies will be initiated after similar studies are completed for chloramine-T and hydrogen peroxide.

Job No. 4: Mutagenicity testing in support of the approval of benzocaine as an anesthetic/sedative.

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Progress: Based on discussions with CVM officials at a meeting on November 15, 1994, CVM will not require mutagenicity testing data to support the approval of benzocaine as an anesthetic/sedative in cultured freshwater fish.

Current Status: Job No. 4 is complete. No further activity is required because data requirements have been met.

Job No. 5: Subacute mammalian toxicity studies in support of the approval of benzocaine as an anesthetic/sedative for all fish in U.S. public fish production.

Progress: CVM officials have identified that only 90-day rodent and 90-day non-rodent feeding studies will be required.

Current Status: UMSC staff is working with CVM Office of Science to draft an Interagency Agreement to contract for these studies. These studies will be contracted after higher priority work with hydrogen peroxide, chloramine-T, and oxytetracycline have been satisfactorily completed.

Job No. 6: Environmental fate and effects studies in support of the approval of benzocaine as an anesthetic/sedative for all fish in public production.

Progress: No activity during July 1, 1995 to December 31, 1995.

Current Status: Environmental fate and effects information is not currently available but may be available from a pharmaceutical sponsor.

STUDY NO. 8: DEVELOPMENT OF HYDROGEN PEROXIDE TO CONTROL FUNGAL INFECTIONS, EXTERNAL BACTERIAL INFECTIONS, AND EXTERNAL PARASITIC INFESTATIONS OF FRESHWATER FISHES.

Objectives: To develop efficacy and target animal safety data to provide fish culturists with effective, safe treatment regimes for hydrogen peroxide to control fungal infections on fish and fish eggs and potentially, for controlling external parasitic infestations and external bacterial infections on freshwater fish.

Job No. 1: Conduct efficacy studies on the use of hydrogen peroxide to control fungal infections of freshwater fish and fish eggs.

Progress: The efficacy of hydrogen peroxide treatments on Atlantic salmon eggs was tested and found to be safe at concentrations up to 1000 L/L. Tests on salmonid eggs have indicated that the most sensitive stage to chemical treatment is the period when the embryo formation begins (Day 5-10 for 12°C).

A study to evaluate the efficacy of hatchery egg incubation systems for delivering hydrogen peroxide treatments has been completed and results are currently being evaluated.

Staff at the UMSC have drafted a protocol to systematically and uniformly induce fungal infections on adult fish. Infected fish will be used to evaluate the efficacy of hydrogen peroxide as a fungicide. Preliminary studies to induce fungal infections on channel catfish and administer treatments were successful.

Current Status: Hydrogen peroxide efficacy studies will continue. Hydrogen peroxide appears to be an effective compound for control of fungal infections on fish and their eggs.

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Job No. 2: Conduct efficacy studies on the use of hydrogen peroxide to control external parasitic infestations and external bacterial infections of freshwater fish at public hatcheries.

Progress: A study protocol entitled "Evaluation of the Efficacy and Safety of Hydrogen Peroxide Exposures to Fish at Fish Hatcheries" has been submitted to hatchery personnel for review. This year hydrogen peroxide efficacy studies are to be conducted on diseased fish at federal and state hatcheries.

Current Status: Efficacy studies will continue throughout this coming year. Preliminary results indicate that hydrogen peroxide may be effective in controlling superficial bacterial infections and parasitic infestations in freshwater fish.

Job No. 3: Conduct target animal safety studies on adult fish and fish eggs with hydrogen peroxide in support of its intended use as an antifungal agent and therapeutic to control external parasitic infestations and external bacterial infections on cultured freshwater fish.

Progress: Target animal safety studies on the eggs of walleye, white sucker, northern pike, channel catfish, common carp, and lake sturgeon were completed. A report is currently being drafted to request an amendment of the current LRP status of hydrogen peroxide. This report requests an increase in the maximum allowable treatment concentration from 500 L/L to 1000 L/L for fish eggs. A protocol to determine the target animal safety of hydrogen peroxide on adult fish is in preparation.

Current Status: Report preparation on completed safety studies will continue this coming year. Hydrogen peroxide appears to be safe for use on a wide variety of fish species and life stages. Data from these studies will be used to support amending the current LRP status of hydrogen peroxide to allow use of concentrations up to 1,000 L/L on fish eggs.

STUDY NO. 9: DEVELOPMENT AND EXECUTION OF STUDIES TO ADDRESS THE CONCEPT OF CROP GROUPING

Objectives: 1) To develop cooperative studies with CVM scientists and university investigators that will result in a reasonable approach to solving problems related to developing extensive residue chemistry data for minor species drug approvals and 2) to develop a course of study to demonstrate similarities and differences in the metabolism and residue chemistry of aquaculture drugs by a broad range of cultured freshwater fish.

Job No. 1: Development of comparative pharmacokinetics and metabolism data for sarafloxacin in rainbow trout and channel catfish.

Progress: No activity during July 1, 1995 to December 31, 1995.

Current Status: A protocol for initial studies is nearing completion and will be initiated when personnel currently working on benzocaine residue studies in rainbow trout are available.

Job No. 2: Development of comparative pharmacokinetics and metabolism data for sarafloxacin in phylogenetically diverse aquaculture species.

Progress: No activity during July 1, 1995 to December 31, 1995.

Current Status: Work on this job will be initiated after more information on the pharmacokinetics and metabolism of sarafloxacin in rainbow trout is complete. Work in other diverse groups of fish will be initiated in 1997.

Job 3: Develop comparative pharmacokinetics and metabolism data for benzocaine in rainbow trout and channel catfish.

Progress: Work continued to evaluate the pharmacokinetics of ¹⁴C-benzocaine in rainbow trout after intravascular administration. These studies are particularly difficult because of the rapid elimination of benzocaine from trout. In a second area, work is being undertaken to implement a physiologically-based pharmacokinetics model for benzocaine. Published physiological values for rainbow trout and channel catfish are being used; tissue to plasma time profile ratios are being developed for both species. In a third study, minor metabolites of benzocaine are being evaluated. Major metabolites of benzocaine (i.e. acetylated benzocaine, para-amino benzoic acid, and acetylated para-amine benzoic acid) have been confirmed in both species.

Current Status: Work in the above study areas will continue.

Job 4: Develop comparative pharmacokinetics and metabolism data in phylogenetically diverse species to support or refute a crop grouping concept for fish.

Progress: The second research work order to support the crop grouping work was initiated September 1995 with Dr. William Hayton, College of Pharmacy, Division of Pharmaceutics, The Ohio State University.

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Current Status: Work to isolate and identify major metabolites of benzocaine is being expanded to include minor species including sturgeon, walleye, and yellow perch.

STUDY NO. 10: NEGOTIATIONS AND CONTRACT COORDINATION

Objectives: To ensure that all data required by CVM for approval through NADAs are developed for the eight priority drugs in a timely, logical, and efficient manner. To coordinate the administration of all contracts by CVM's Office of Science to ensure efficiency, timelessness, and acceptability of data to CVM. To track and report the progress of all of studies and ensure that they are proceeding for approval in a timely, logical, and efficient manner. To assemble and submit NADAs for approval to CVM.

Job No. 1: Determine data requirements for approval of each candidate drug.

Progress: Discussions between UMSC and CVM to obtain a sponsor for benzocaine resulted in a decision to contact prospective sponsors and invite them to consider sponsorship of benzocaine NADAs. Each candidate will be asked what their contributions to the data package for an NADA would be.

CVM has indicated that the INADs for the use of oxytetracycline as a marking agent will continue, but that CVM is close to a decision on extending the NADA for that purpose to species other than Pacific salmon.

After several discussions with CVM and interested parties on the current status of hydrogen peroxide as a low regulatory priority drug, a decision was made to consider pursuing an NADA. An environmental report prepared for the approval of hydrogen peroxide in Canada was reformatted to CVM requirements and purchased by UMSC for submission into a veterinary master file. A meeting was held with representatives of the potential sponsor of a NADA on hydrogen peroxide, Eka Nobel, Inc. and UMSC on December 7, 1995 to discuss the data requirements, procedures, and status of data for a joint effort toward a NADA.

UMSC representatives met with the current sponsor of a NADA on chloramine-T, Akzo Nobel Chemicals, Inc., on August 16, 1995 to discuss the status of data development and procedures leading to a NADA. Discussions have also been held with another potential sponsor of a NADA on chloramine-T, H & S Chemical Company, Inc., concerning procedures for implementing a NADA.

Several times since June 1, 1995, discussions were held with UMSC staff and CVM regarding CVM's aquaculture workload plan and the status and direction for formalin, chloramine-T, hydrogen peroxide, and oxytetracycline. Contact was made in November 1995 with French officials who are interested in sharing information on drugs of mutual interest.

Current Status: Progress has been made on interactions with current or potential sponsors of NADAs for chloramine-T and hydrogen peroxide and letters will soon go out to potential sponsors of benzocaine. Negotiations and discussions continue with CVM regarding data requirements for all IAFWA drugs.

Job No. 2: Coordinate the administration of contracts by CVM's Office of Science.

Progress: UMSC has interacted with Dr. David Batson (CVM) several times this half year to develop an interagency agreement (IAG) with the Office of Science to administer and monitor the toxicological research to be performed outside of the NBS. Dr. Batson prepared a draft agreement (dated November 9, 1995) for review. It was decided that studies would be performed by commercial firms.

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Current Status: The IAG will be finalized soon; however, the decision to implement studies on benzocaine will be delayed until the budget for fiscal year 1996 for UMSC has been clarified.

Job No. 3: Track the progress of all studies and summarize and report the data.

Progress: The first annual report of progress on the IAFWA project was written for the period from July 1, 1994 to June 30, 1995 and distributed to all IAFWA project participants and stake holders. Presentations were made on the IAFWA project to the U.S. Trout Farmers Association, National Research Support Program Number 7, INAD/NADA Coordinators meeting in November 1995, and the Canadian Salmon Health Consortium Executive Director.

Current Status: Appropriate progress reports have been and will continue to be presented to the IAFWA project participants and stake holders.

Job No. 4: Assemble and submit NADA packages to FDA for approval.

Progress: Personnel of the UMSC held a meeting on November 1-2, 1995 in Rockville, MD with INAD Coordinators. The objectives of the meeting were to: (1) increase communications between coordinators, (2) develop working relationships, (3) review the roles and responsibilities of INAD\NADA coordinators, (4) coordinate the data generation for each drug, (5) consolidate INADs where possible, (6) determine the general format for INAD\NADA submissions and (7) exchange information on current progress and any significant research findings for each drug. Twenty-two INAD\NADA coordinators and five CVM representatives participated in the workshop. The goals of the workshop were either met or plans were set in motion to accomplish the remainder.

Letters went out to all holders of both disclosed and undisclosed (through CVM) INADs of chloramine-T that an effort would be made to consolidate and coordinate these INADS, develop label claims, and identify pivotal study sites at an upcoming meeting on INAD\NADAs in Council Bluffs, Iowa, on February 6-8, 1996.

A NADA submission was made to CVM on December 15, 1995 of a report entitled "Safety of Formalin Treatments on Fish Eggs". This submission will be reviewed by CVM along with the data on the use of formalin as a parasiticide on hybrid striped bass developed at Auburn University. These submissions will hopefully lead to the extension of the formalin NADA to additional species and, thus, remove the need for INADs on formalin.

Current Status: UMSC is looking forward to a decision in the near future on extension of the formalin NADA to all cultured freshwater fishes; thus, eliminating the need for INADs. A major coordination meeting will be held in February 1996 in Council Bluffs, Iowa to discuss the new CVM workload.