Final Federal Aid Report
Federal-State Aquaculture Drug Approval Partnership Project

a project of the

International Association of Fish and Wildlife Agencies (IAFWA)

by

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EXECUTIVE SUMMARY

In the beginning, the toolbox of available therapeutants and anesthetics for public fish production was virtually empty. After eight years of effort, tremendous progress has been made and 11 new label claims for six drugs are nearing completion. Considering that the International Association of Fish and Wildlife Agencies' Federal-State Aquaculture Drug Approval Partnership Project (Project) participants expended only $12 million in eight years to support those 11 label claims, for six drugs, for multiple fish species, and for multiple diseases, the results are indeed remarkable. To put this into some perspective, pharmaceutical companies usually expect to spend $12 million or more over a ten-year period, to secure one label claim, for one drug, for one species, and for one disease incidence! Administrators and scientists at the U.S. Food and Drug Administration's Center for Veterinary Medicine (CVM) frequently compare the multi-state/federal shoestring effort with these pharmaceutical company investments, and marvel at what has been accomplished.

The Project is now completed in its present form. New Animal Drug Application submissions to CVM to support original or supplemental approvals for Project drugs are the result of efforts by the U.S. Geological Survey's Upper Midwest Environmental Sciences Center (UMESC), U.S. Department of Agriculture's Harry K. Dupree Stuttgart National Aquaculture Research Center (SNARC), U.S. Fish and Wildlife Service's (FWS) Bozeman National Investigational New Animal Drug (INAD) Office (NIO), other public agencies such as state natural resources agencies, the private aquaculture sector, company sponsors, and the National Coordinator for Aquaculture New Animal Drug Applications (National NADA Coordinator).

Building on this important foundation, work will continue on additional label claims as well as new drugs, using appropriated funds for UMESC, SNARC, NIO, and others, including the pharmaceutical and chemical company sponsors. Multi-State Conservation Grant funds have also supported aspects of this work, and may provide more future funding. UMESC will continue involvement in drug approvals as long as the states request it. The National NADA Coordinator will continue to coordinate all aquaculture drug approvals. A larger expanded future effort is also being planned for the FWS Division of Fisheries and Habitat Conservation. Drug sponsors are starting to step forward to play a more active role in the drug approval process.

SUCCESSES OF THE FEDERAL-STATE AQUACULTURE DRUG APPROVAL PARTNERSHIP PROJECT

Label Claims Nearing Successful Completion

1. Chloramine- T--mortality from bacterial gill disease on all freshwater-reared salmonids
2. Copper sulfate--*Ichthyophthirius* on catfish in earthen ponds
3. Florfenicol--mortality from furunculosis in salmonids

4. Florfenicol--mortality from enteric septicemia in catfish
5. Formalin--mortality from saprolegniasis on all fish
6. Hydrogen peroxide--mortality from saprolegniasis on all fish eggs
7. Hydrogen peroxide--mortality from saprolegniasis on all fish
8. Hydrogen peroxide--mortality from bacterial gill disease on all freshwater-reared salmonids
9. Oxytetracycline--mortality from systemic columnaris disease in certain freshwater-reared salmonids
10. Oxytetracycline--mortality from systemic coldwater disease in all freshwater-reared salmonids, and
11. Oxytetracycline--otolith marking of all fish by immersion

General Successes

1. Identified, obtained, replaced, and retained committed company sponsors for all eight Project drugs after starting and finishing with only one drug (formalin) being covered by its original sponsors
2. Generated data and coordinated efforts that resulted in approved supplemental NADA for formalin to control fungi on the eggs of all fish and external protozoa and monogenetic trematodes on all fish
3. Coordinated efforts for 11 label claims for six drugs that are nearing completion toward approval
4. Identified alternate drugs and sponsors to replace sarafloxacin and benzocaine
5. Obtained new sponsors to replace sponsors for chloramine- T and oxytetracycline
6. Developed Cooperative Research and Development Agreements with company sponsors for AQUI-S™, copper sulfate, chloramine-T, and florfenicol
7. Identified data requirements for label claims for each of the eight Project drugs
8. Developed acceptable protocols and executed studies accordingly
9. Submitted numerous technical section data packages for all eight Project drugs
10. Had acceptance of numerous data submissions for anticipated new or supplemental NADA approvals
11. Expecting broader approvals for hydrogen peroxide and oxytetracycline beyond 2002
12. Expecting limited approvals for chloramine-T, copper sulfate, and florfenicol beyond 2002; limited new approvals on potassium permanganate and AQUI-S™ beyond 2002
13. Established compassionate INAD program that has allowed widespread access to Project drugs while NADAs are being completed

14. Established a science-based approach for broad drug approvals for aquaculture drugs by crop grouping research in consultation with scientists and administrators at CVM

Abbreviations and Acronyms used in this report

BGD	Bacterial Gill Disease
CRADA	Cooperative Research and Development Agreement
CVM	Center for Veterinary Medicine, Food and Drug Administration, U.S. Department of Health and Human Services
DAWG	Drug Approval Working Group, International Association of Fish and Wildlife Agencies
DCI	Data Call-in
EA	Environmental Assessment
EPA	U.S. Environmental Protection Agency
FWS	Fish and Wildlife Service, U.S. Department of the Interior
IAFWA	International Association of Fish and Wildlife Agencies
INAD	Investigational New Animal Drug exemption
JSA	Joint Subcommittee on Aquaculture
LRP	Low Regulatory Priority status
NADA	New Animal Drug Application
NIO	Bozeman National Investigational New Animal Drug Office, Fish and Wildlife Service, U.S. Department of the Interior
NTP	National Toxicology Program
NRSP-7	National Research Support Project Number 7
p-TSA	para-toluenesulfonamide
SNARC	Harry K. Dupree Stuttgart National Aquaculture Research Center, Agricultural Research Service, U.S. Department of Agriculture
UMESC	Upper Midwest Environmental Sciences Center, Biological Resources Discipline, U.S. Geological Survey, U.S. Department of the Interior

FINAL REPORTS FOR EACH STUDY IN THE FEDERAL-STATE AQUACULTURE DRUG APPROVAL PARTNERSHIP PROJECT

Study No. 1: Extend the approval of formalin as a therapeutant to control fungal infections on eggs and fish currently produced in public aquaculture facilities

A. Initial status:
   1. Had previous NADA approval for control of fungi on salmonid, trout, and esocid eggs
   2. Had previous NADA approval for control of external protozoa and monogenetic trematodes on trout, salmon, catfish, largemouth bass, and bluegill
   3. Had three company sponsors for previous NADA approvals

B. Course of action:
   1. UMESC established and supervised initial compassionate INAD within FWS to gather efficacy data to control saprolegniasis (fungal infections) on all fish and their eggs
   2. UMESC conducted target animal safety studies to support an "all fish eggs" claim; accepted by CVM
   3. UMESC conducted pivotal and supporting efficacy studies to control mortality from saprolegniasis on all fish eggs; accepted by CVM
   4. July 1997--UMESC conducted Data call-in for efficacy data from compassionate INAD for control of mortality from saprolegniasis on fish; submitted September 1998 to CVM; data declared supportive by CVM
   5. UMESC and CVM Office of Research conducting pivotal efficacy studies to control mortality from saprolegniasis on channel catfish and rainbow trout
   6. NRSP-7 gathered data for supplemental NADA for formalin to control fungi on <u>all</u> fish eggs and external protozoa and monogenetic trematodes on <u>all</u> fish; accepted by CVM
   7. Western Chemical Inc. submitted supplemental NADA for formalin to control fungi on <u>all</u> fish eggs and external protozoa and monogenetic trematodes on <u>all</u> fish; accepted by CVM
   8. Natchez Animal Supply Company recently submitted supplemental NADA for formalin to control fungi on <u>all</u> fish eggs and external protozoa and monogenetic trematodes on <u>all</u> fish; accepted by CVM

C. Summary of accomplishments:

1. Submissions have been made to support the NADA approval of formalin in all technical sections; accepted as complete by CVM--target animal safety for all fish eggs, efficacy for control of fungus on all fish eggs
2. First major successes of Project--1998 supplemental NADA approval for formalin to control fungi on the eggs of all fish
3. First major successes of Project--1998 supplemental NADA approval for formalin to control external protozoa and monogenetic trematodes on all fish
4. Label claim for an NADA on formalin nearing completion--mortality from saprolegniasis on all fish; only efficacy technical section remains to be completed
5. Retained three company sponsors for NADAs on formalin; two company sponsors obtained supplemental NADAs

Study No. 2: Expansion of the oxytetracycline feed additive formulation for control of flexibacteriosis [flavobacteriosis=columnaris and coldwater diseases] on cold, cool, and warmwater fishes, and extension of the treatment of certain bacterial diseases and for otolith marking on coolwater and warmwater species

A. Initial status:
   1. Had previous NADA approval for control of bacterial hemorrhagic septicemia and pseudomonas disease in catfish
   2. Had previous NADA approval for control of ulcer disease, furunculosis, bacterial hemorrhagic septicemia, and pseudomonas disease in salmonids
   3. Had previous NADA approval to mark otoliths of Pacific salmon in feed
   4. Had Pfizer, Inc. as company sponsor of previous NADA approvals

B. Course of action:
   1. NIO conducted pivotal efficacy studies to control mortality from systemic coldwater disease in all freshwater-reared salmonids; accepted by CVM
   2. NIO conducted pivotal efficacy studies to control mortality from systemic columnaris disease in certain salmonids reared in freshwater; accepted by CVM
   3. NIO gathered supportive efficacy data through compassionate INAD for above two diseases in salmonids after taking over initial compassionate INAD from UMESC
   4. UMESC established and supervised initial compassionate INAD within FWS to gather efficacy data to control flavobacteriosis and other systemic bacterial diseases in all fish
   5. October 1997--UMESC conducted Data call-in for efficacy data from compassionate INAD for control of mortality from *Aeromonas sp*, bacterial coldwater disease,

systemic columnaris disease and enteric redmouth; submitted to CVM, January 1999; data declared supportive by CVM

6. UMESC provided analytical support for analysis of oxytetracycline in feed for pivotal efficacy studies conducted by NIO
7. UMESC developed analytical methods for OTC residues in tissues, bridged method to official microbial inhibition assay, and used methods to conduct marker residue depletion studies in fish
8. UMESC conducted oxytetracycline residue depletion studies from salmonids below 9°C; accepted by CVM
9. UMESC conducted oxytetracycline residue depletion studies from representative cool water fish species (walleye and northern pike) to allow an "all fish" label claim; accepted by CVM
10. UMESC conducted oxytetracycline target animal safety studies in walleye, hybrid striped bass, and yellow perch to allow an "all fish" label claim; submitted to CVM
11. UMESC developing amended environmental assessment for oxytetracycline to allow discharge of effluent into public waters; will be submitted to CVM by December 2002
12. UMESC conducting pivotal efficacy studies for control of systemic columnaris disease in coolwater and warmwater fish
13. NRSP-7 prepared and submitted supplemental NADA for marking otoliths by immersion on all fish; accepted by CVM
14. December 1996--Tolerance for oxytetracycline increased from 0.1 ppm to 2.0 ppm in edible tissue by CVM

C. Summary of accomplishments:

1. Submissions have been made to support the NADA approval of oxytetracycline in all technical sections; accepted as complete--human food safety for all fish and below 9°C, target animal safety studies in coolwater and warmwater fish, and efficacy for two systemic diseases in salmonids
2. Label claim for an NADA on oxytetracycline nearing completion--mortality from systemic columnaris disease in certain freshwater-reared salmonids
3. Label claim for an NADA on oxytetracycline nearing completion--mortality from systemic coldwater disease in all freshwater-reared salmonids
4. Label claim for an NADA on oxytetracycline nearing completion--otolith marking of all fish by immersion
5. Identified, obtained, and retained new company sponsor (Phibro Animal Health) to replace Pfizer, Inc. for an NADA on oxytetracycline

Study No. 3: Approval of copper sulfate as a therapeutant to control external protozoan and metazoan parasitic, bacterial, and fungal diseases of cultured food fish

A. Initial status:
   1. Was registered as an aquatic herbicide and algicide by EPA
   2. Had no company sponsor for NADA

B. Course of action:
   1. CVM declared mammalian safety data to be acceptable based on EPA registration data
   2. SNARC conducted a literature review for efficacy data on copper sulfate; data declared as supportive by CVM for *Ichthyophthirius* for all fish
   3. SNARC conducted pivotal efficacy studies for control of *Ichthyophthirius* on catfish; accepted by CVM
   4. SNARC conducted residue chemistry study in channel catfish; accepted by CVM
   5. SNARC conducted target animal safety study on channel catfish; revision to be submitted to CVM
   6. SNARC developed environmental assessment for use of copper sulfate in earthen ponds; revision to be submitted to CVM
   7. SNARC conducted environmental study; to be submitted to CVM
   8. Phelps Dodge Refining Corporation developed and submitted product chemistry package; accepted by CVM

C. Summary of accomplishments:
   1. Submissions have been made to support the approval of copper sulfate in all technical sections; accepted as complete by CVM (product chemistry, mammalian safety, human food safety, efficacy for control of *Ichthyophthirius* on all fish)
   2. Label claim for an NADA on copper sulfate nearing completion--*Ichthyophthirius* on catfish in earthen ponds
   3. Identified, obtained, and retained company sponsor (Phelps Dodge Refining Corporation) for an NADA on copper sulfate

Study No. 4: Approval of chloramine-T as a drug to control bacterial gill disease on salmonids and flexibacteriosis [flavobacteriosis=columnaris and coldwater diseases] on coldwater, coolwater, and warmwater fish species

A. Initial status:
    1. Had no previous approvals or registrations in the United States for aquatic uses
    2. Had no company sponsor for NADA

B. Course of action:
    1. NIO conducted pivotal efficacy studies to control mortalities related to bacterial gill disease in all salmonids reared in freshwater; accepted by CVM
    2. NIO conducted and submitted target animal safety studies on salmonids
    3. UMESC established and supervised initial compassionate INAD within FWS to gather efficacy data to control bacterial gill disease and external columnaris disease in all fish
    4. November 1997--UMESC conducted efficacy Data call-in of INAD; submitted to CVM, July 1998; declaration by CVM that all submitted data is supportive for control of bacterial gill disease in all salmonids reared in freshwater and tiger muskie
    5. UMESC developed simple analytical field method to monitor efficacy studies; accepted by CVM to document concentrations of chloramine-T in hatchery waters; supported pivotal efficacy field trials
    6. UMESC conducted and submitted analytical data to address human food safety technical sections in marker residue identification, determinative method development and validation, residue depletion studies in representative cold, cool and warm water fish species, and development/validation of a confirmative method for marker residue in cultured freshwater fish
    7. UMESC conducted and submitted target animal safety studies on cool and warm water fish
    8. UMESC conducted and submitted environmental summary into public master file to support use of chloramine-T in public hatcheries seeking to discharge effluents
    9. UMESC developing proprietary environmental assessment for sponsor to submit
    10. Akzo Nobel Chemicals, Inc. (now Axcentive bv) submitted mammalian safety studies; some accepted by CVM
    11. March 2001--CVM notified INAD holders that CVM had possible concerns for carcinogenicity and would not renew the INADs until CVM received new information that addressed those concerns.
    12. Axcentive bv conducted two genotoxicity studies; accepted by CVM

C. Summary of accomplishments:

1. Submissions have been made to support the approval of chloramine-T in all technical sections except product chemistry; accepted as complete by CVM--efficacy to control mortalities related to bacterial gill disease in all salmonids reared in freshwater; although CVM has reviewed and found data to be acceptable, the agency will not accept as complete the human food safety data until the mammalian safety technical section is declared complete
2. Label claim for an NADA on chloramine- T nearing completion--mortality from bacterial gill disease on all freshwater-reared salmonids
3. Identified and obtained Akzo Nobel Chemicals, Inc. as company sponsor for chloramine-T
4. Obtained and retained new company sponsor (Axcentive bv) to replace Akzo Nobel Chemicals, Inc. for an NADA on chloramine-T

Study No. 5: Approval of sarafloxacin hydrochloride [now florfenicol] as a drug to control flexibacteriosis [flavobacteriosis=columnaris and coldwater diseases] and furunculosis in freshwater fish

A. Initial status:
   1. Had no previous approvals or registrations in the United States for aquatic uses
   2. Had Abbott Laboratories as company sponsor for an NADA on sarafloxacin

B. Change in status:
   1. 1995--funds transferred to oxytetracycline pending resolution of microbial resistance related to fluoroquinolones
   2. 1997--CVM indicated that no fluoroquinolone (e.g., sarafloxacin) could gain approval since that class of drugs are extremely important to human health and CVM was concerned about antimicrobial resistance developing as a result of use in animals
   3. December 1997--Schering-Plough Animal Health agreed to allow development of their antibacterial, florfenicol, for U.S. aquaculture
   4. December 1997--Project stakeholders voted to replace sarafloxacin with florfenicol
   5. March 2000--DAWG diverted funds from florfenicol to other Project drugs so that there would be some form of approvals for each drug and because of concern that florfenicol could not pass the antimicrobial resistance hurtle

C. Course of action:
   1. NIO conducting efficacy studies under limited INAD

2. UMESC validated method to analyze florfenicol in fish feeds to support efficacy studies
3. UMESC completed a robust analytical method for florfenicol in plasma of multiple fish species as well as florfenicol in tissues of a number of fish to support crop-grouping work.
4. UMESC conducted target animal safety study on channel catfish under CRADA with Schering-Plough Animal Health; submitted to sponsor
5. Schering-Plough Animal Health developing complete data package for control of furunculosis in salmonids and enteric septicemia in catfish; proprietary status

D. Summary of accomplishments:
   1. Submissions made by Schering-Plough Animal Health for florfenicol but proprietary status information
   2. Label claim for an NADA on florfenicol nearing completion--mortality from furunculosis in salmonids
   3. Label claim for an NADA on florfenicol nearing completion--mortality from enteric septicemia in catfish
   4. Convinced Schering-Plough Animal Health to pursue aquaculture NADA approvals in the United States for florfenicol; obtained and retained the company as company sponsor for an NADA on the drug

Study No. 6: Approval of potassium permanganate as a therapeutant to control external protozoan and metazoan parasitic, bacterial, and fungal diseases of cultured food fish

A. Initial status:
   1. Had no previous approvals or registrations in the United States for aquatic uses
   2. Had no company sponsor for NADA

B. Course of action:
   1. Carus Chemical Company developed and submitted product chemistry package; revision in preparation
   2. SNARC conducted residue chemistry study (human food safety) in channel catfish; accepted by CVM
   3. SNARC conducted target animal safety study on channel catfish; to be submitted
   4. SNARC conducted efficacy study for control of *Ichthyophthirius* on catfish; to be submitted

5. Arkansas State University obtained outside funds to conduct environmental safety studies for pond and flow-through systems; studies in progress

C. Summary of accomplishments:
   1. Submissions have been made to support the approval of potassium permanganate in two technical sections; accepted as complete by CVM--human food safety, mammalian safety accepted as part of human food safety
   2. Identified, obtained, and retained Carus Chemical Company as company sponsor for an NADA on potassium permanganate

Study No. 7: Approval of benzocaine [now AQUI-SÔ] as an anesthetic and sedative for fish

A. Initial status:
   1. Had no previous approvals or registrations in the United States for aquatic uses
   2. Had no company sponsor for NADA

B. Change in status:
   1. August 1997--Project stakeholders voted to replace benzocaine with AQUI-S™ because AQUI-S™ had a sponsor, was more likely to obtain a zero withdrawal time, and would not require expenditure of Project funds for mammalian safety studies
   2. March 2000--DAWG decided to continue research on AQUI-S™ whose status as a potential carcinogen was not known, but whose sponsor concluded that the active ingredient is safe based on: (1) an understanding of metabolic pathways that support safety, (2) agreement on safety by independent experts, (3) supportive preliminary results of a parallel NTP study, (4) similar results on a related active ingredient, eugenol, and (5) similar toxicological studies showed no adverse effect.
   3. August 2001--DAWG redirected UMESC funds for efficacy and target animal safety studies to residue chemistry and directed NIO to conduct efficacy and target animal safety studies with outside funds
   4. Summer 2001--AQUI-S New Zealand LTD. decided to stay with the original active ingredient and not switch to a related ingredient; indecision delayed development of data

C. Course of action:
   1. AQUI-S New Zealand Ltd. planning product chemistry
   2. AQUI-S New Zealand Ltd. monitoring NTP studies on AQUI-S™

3. November 1998--AQUI-S New Zealand Ltd. submitted an environmental summary to CVM
4. AQUI-S New Zealand Ltd. completed an environmental biodegradation study in freshwater and salt water; to be submitted to CVM
5. AQUI-S New Zealand Ltd. and UMESC initiated environmental assessment
6. AQUI-S New Zealand Ltd. conducted target animal safety studies on Atlantic salmon and efficacy studies on Atlantic salmon; to be submitted to CVM
7. NIO conducting target animal safety studies on salmonids
8. NIO conducting efficacy studies on all fish
9. Before change in anesthetic (1994 to 1996), UMESC conducted several residue chemistry studies on benzocaine
10. July 1997--UMESC completed an efficacy and safety evaluation that was sent to all stakeholders for their decision on whether benzocaine or AQUI-S™ should be the Project anesthetic
11. UMESC conducting residue chemistry studies on salmonids

D. Summary of accomplishments:
    1. Obtained an active sponsor for a potential zero withdrawal anesthetic (AQUI-S™) in place of a an anesthetic (benzocaine) that did not have a company sponsor, may not have had a zero withdrawal time, and would have required major expenditure of Project funds for mammalian safety studies
    2. No submissions because indecision about formulation of AQUI-S™ by company sponsor impeded progress toward completion; however, plans and progress made for developing data for NADA approval

Study No. 8: Development of the use of hydrogen peroxide to control fungal infections, external bacterial infections, and external parasitic infestations of freshwater fishes

A. Initial status:
    1. Had no previous approvals or registrations in the United States for aquatic uses
    2. Had LRP status
    3. Had no company sponsor for NADA

B. Change in status:
    1. Currently retains its current LRP status to control and prevent saprolegniasis on fish and fish eggs

2. Pursuing an NADA for hydrogen peroxide based on request by company sponsor (Eka Chemicals Inc.) in January 1996 for an NADA on hydrogen peroxide
3. CVM stated in June 1995 that LRP status would not apply to external antibacterial or parasiticide uses but would require an NADA approval

C. Course of action:

1. CVM accepted human food safety technical section as complete (mammalian safety and residue chemistry)
2. UMESC conducted target animal safety studies for "all fish"; accepted by CVM
3. UMESC conducted target animal safety studies for "all fish eggs"; accepted by CVM
4. UMESC conducted pivotal efficacy studies to control mortality for bacterial gill disease for all freshwater-reared salmonids; accepted by CVM
5. UMESC conducted efficacy studies to control external protozoan infestations for all salmonids; data accepted as supportive by CVM
6. UMESC conducted pivotal efficacy studies to control mortality from external fungal infections on all fish eggs; data on cold and cool water fish eggs accepted by CVM; additional efficacy data on warmwater fish eggs to be submitted to CVM
7. UMESC established a compassionate INAD to gain supportive efficacy data for control of external fungal, bacterial, and parasitic diseases on all fish, especially coolwater and warmwater fish
8. UMESC conducting pivotal efficacy studies to control mortality from saprolegniasis on channel catfish and rainbow trout to gain an "all fish" label claim
9. UMESC developed and submitted environmental assessment of hydrogen peroxide use by hatcheries with effluent discharge submitted; additional information (*Daphnia* chronic reproduction study) requested by CVM
10. Eka Chemicals Inc. submitted an initial product chemistry data package and a revision

D. Summary of accomplishments:

1. Submissions have been made to support the approval of hydrogen peroxide in all technical sections; accepted as complete by CVM--mammalian safety, human food safety, target animal safety to all fish and fish eggs, efficacy for control of bacterial gill disease for all freshwater-reared salmonids and control mortality from external fungal infections on cold and cool water fish eggs
2. Label claim for an NADA on hydrogen peroxide nearing completion--mortality from saprolegniasis on all fish eggs

3. Label claim for an NADA on hydrogen peroxide nearing completion--mortality from saprolegniasis on all fish
4. Label claim for an NADA on hydrogen peroxide nearing completion--mortality from bacterial gill disease on all freshwater-reared salmonids
5. Identified, obtained, and retained Eka Chemicals Inc. as company sponsor for an NADA on hydrogen peroxide

Study No. 9: Development of and execution of studies to address the concept of crop grouping

A. Initial status:
   1. No crop grouping research for residue chemistry studies on fish for either waterborne or oral drugs

B. Change in status:
   1. Because of unavailability of radio labeled florfenicol and the unanticipated need for human food safety for AQUI-S™, efforts on florfenicol were terminated and all effort was redirected to conduct AQUI-S™ residue studies

C. Course of action:
   1. 1995--UMESC presented crop grouping concept to panel of peer experts
   2. Ohio State University, under a contract from UMESC, conducted comparative pharmacokinetic and metabolism studies for benzocaine in rainbow trout, yellow perch, and channel catfish
   3. Ohio State University, under a contract from UMESC, conducted comparative pharmacokinetic and metabolism studies for benzocaine in phylogenetically diverse species to support a crop grouping concept for fish
   4. UMESC conducted initial analytical method development studies with florfenicol and initiated early modeling efforts
   5. August 2000--UMESC and Ohio State University held seminar at CVM Office of Research to discuss results of research efforts on crop grouping

D. Summary of accomplishments:
   1. Results of benzocaine studies indicate that there are more similarities than differences in the manner in which diverse groups of fish handle benzocaine.
   2. CVM is taking under consideration the concept of crop grouping for aquaculture drugs

Study No. 10: Negotiations and contract coordination

A. Initial status:
    1. No negotiations or contract coordination underway for NADAs on any of the eight Project drugs
    2. No technical section submissions for NADAs on any of the eight Project drugs
    3. Only two company sponsors for NADAs (formalin and oxytetracycline)

B. Change in status:
    1. 1995--UMESC funding and drug approval program threatened with elimination; saved
    2. 1996--SNARC transferred to U.S. Department of Agriculture; UMESC transferred to U.S. Geological Survey
    3. 1997--DAWG formed to aid the Project to achieve its goal of obtaining NADA approvals for drugs of priority to U.S. public aquaculture and consider whether the Project should be extended beyond June 30, 1999 with the intent of developing data to support the approval of an additional oral antibacterial other than oxytetracycline.
    4. Fiscal Year 1999--UMESC funding and drug approval program threatened with elimination; saved
    5. Amendment No. 1: 1997--mid-point course correction because of (1) changes in original contribution estimates, (2) impacts of policy decisions by CVM, (3) reinventing government and downsizing, and (4) revised study objectives based on assessment of the original Project goals.
    6. Amendment No. 2: 1999--extension of the grant to continue through Years 6, 7, and 8 (July 1, 1999 to June 30, 2002).
    7. Amendment No. 3: 2000--changed the Project scope by updating status relative to original objectives, providing additional information requested by CVM, and clarifying objectives for Year 7 and 8. Work on florfenicol was discontinued and effort redirected to other priority drugs at the direction of DAWG
    8. Amendment No. 4: 2001--incorporated revisions that generally reflected additions or changes to the work plans required by CVM in order to fulfill requirements of technical sections in environmental safety, human food safety, target animal safety, and efficacy for the Project drugs AQUI-S™, chloramine-T, hydrogen peroxide, and oxytetracycline. In addition to elements required by CVM, a portion of work planned for Study 9, Crop Grouping, was redirected by DAWG in order to address Project deficiencies in the lack of adequate pivotal and supporting efficacy data. Study 10,

Negotiations and Coordination was expanded by the addition of three elements to facilitate conclusion of the Project.

C. Course of action:

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

a. The National NADA Coordinator (1) 1994--wrote the initial INAD exemption protocols that acted as templates for future protocols for Project, (2) 1994 to present--discussed with CVM, UMESC, SNARC, and NIO, the status and direction or developing data for NADA approvals and negotiated with CVM regarding label claims and regulatory requirements, (3) 1994 to present--helped determine all the data requirements and data gaps for NADAs for the eight Project drugs through interaction with CVM and where and how to get the data generated, (4) 1994 to present--solicited and obtained new company sponsors for all eight Project drugs and their replacements; helped the company sponsors develop Research and Development Plans, (5) 1994 to present--interacted with company sponsors of all Project drugs, helped guide sponsors toward company submissions, arranged meetings with CVM, and prepared minutes to those meetings, (6) 1996--prepared status report on AQUI-S™ and benzocaine, (7) 1996--co-chaired workshop with Dr. William Gingerich of UMESC to establish criteria for pivotal efficacy study protocols on all drugs and select sites for pivotal efficacy studies on chloramine- T; wrote minutes to workshop and distributed them, (8) 1997 to present--analyzed, presented status of Project drugs, and offered solutions to data gaps to DAWG twice annually and prepare minutes to all meetings, (9) 1997--sent survey to all Project stakeholders and cooperators for assessment and opinion on whether to replace benzocaine with AQUI-S™, (10) 1997--solicited and secured through seminars the commitment of company sponsors for oxytetracycline and florfenicol, (11) 1997--sent survey to Project stakeholders regarding the potential replacement of sarafloxacin with florfenicol; analyzed results, (12) 1998-1999--developed strategy to resolve mammalian safety data requirements for chloramine-T by suggesting an early life stage approach; CVM reduced data requirements, (13) 1999 to present--developed several initiatives to gain additional investigators for the development of efficacy data, (14) 2000--solicited and secured through a seminar the commitment of the new company sponsor to continue to support the development of its chloramine- T product, (15) 2001--prepared supplemental NADA submission for formalin sponsor, (16) 2001 to present--

solicited and secured through a seminar the commitment of the company sponsor for diquat to meet states' unmet drug needs, (17) 2001 to present--solicited and secured the commitment of the company sponsor for Romet-30® to meet states' unmet drug needs, (18) 2001--met with CVM and company sponsor on resolving issues related to mammalian safety of chloramine-T and transferred information that was not confidential to affected entities, (19) 2001 to present--invited nine current and potential company sponsors to FWS workshop and have continued to follow up on possible development of additional products, (20) 2001 to present--requested identification of unmet label claim needs from the state fish chiefs; analyzed results, (21) 2001 to present--requested fish production data from all 50 state fish chiefs for market information for current and potential company sponsors; sent responses to FWS, and (22) 2002--solicited and secured through a seminar the commitment of the company sponsor to continue support of the development of their potassium permanganate product for aquaculture

b. NIO determined efficacy technical section data requirements for AQUI-S™, chloramine-T (and target animal safety), florfenicol, and oxytetracycline in discussions with CVM and the National NADA Coordinator
c. SNARC determined technical section data requirements for copper sulfate and potassium permanganate in discussions with CVM and the National NADA Coordinator
d. UMESC (1) determined data requirements for AQUI-S™, chloramine-T, florfenicol, formalin, hydrogen peroxide, oxytetracycline, and crop grouping in discussions with CVM and the National NADA Coordinator, (2) 1994 to present--wrote pivotal efficacy protocols that acted as templates for future protocols for other participants in the Project and used these protocols for efficacy studies, (3) 1996--initiated and co-chaired workshop to establish criteria for pivotal efficacy study protocols on all drugs and select sites for pivotal efficacy studies on chloramine- T, (4) helped NIO establish a quality assurance program and provided protocols for target animal safety studies on chloramine-T, (5) worked with sponsors of AQUI-S™, chloramine-T, and hydrogen peroxide to determine data requirements and existence of data for environmental assessments, (6) held a work planning/coordination meeting (November 1998) to evaluate progress being made on the technical sections for each drug and made revisions to existing work plans where necessary, and (7) surveyed public and private U.S. aquaculture facilities for how drugs are used to

help in developing environmental assessments for AQUI-S™, chloramine-T, florfenicol, hydrogen peroxide, potassium permanganate, and oxytetracycline

e. Sponsors determined product chemistry technical section data requirements for AQUI-S™ (and other technical sections), chloramine-T (and mammalian safety), copper sulfate, florfenicol (all technical section data requirements), hydrogen peroxide, and potassium permanganate in discussions with CVM and the National NADA Coordinator

2. Job No. 2: Coordinate the administration of contracts
    a. National NADA Coordinator in 2001 analyzed rankings for proposals for funding from the Multi-State Conservation Grants
    b. SNARC established CRADA with the sponsor of copper sulfate
    c. UMESC (1) 1994-1996--developed Interagency Agreement with CVM's Office of Science to conduct studies on benzocaine and other drugs as needed, (2) 1995-2000--developed work orders with Ohio State University for crop grouping research on benzocaine, (3) 1996 to present--initiated and continued Interagency Agreement with U.S. Department of Agriculture to partially fund the National NADA Coordinator, (4) 1999--established Cooperative Research and Development Agreement (CRADA) with the sponsor of AQUI-S™, (5) 1999--established CRADA with the sponsor of chloramine-T, (6) 2001--established CRADA with the sponsor of florfenicol, and (7) 2001--developed Interagency Agreement with CVM's Office of Research to develop and validate a confirmatory method for p-TSA
3. Job No. 3: Track the progress of all studies and summarize and report the data
    a. National NADA Coordinator (1) 1994 to present--co-chaired FWS annual INAD meetings, (2) 1999 to present--Website established and maintained through efforts of U.S. Department of Agriculture, (3) 1994 to present--organized and chaired many sessions at national and regional aquaculture meetings on participating in INADs, identifying label claim needs, criteria for pivotal efficacy studies, and potential pivotal efficacy sites, (4) 1994 to present--presented information on the Project at all the Mid-Continent Workshops, (5) 1994 to present--provided minutes to all meetings with CVM, company sponsors, Drug Approval Working Group, conference calls, and workshops on Project drugs, (6) 1994 to present--helped summarize the data and prepared, coordinated, and edited the annual and midyear reports for the Project and work plans for UMESC, (7) helped establish an initial tracking system for the funds and progress on studies, and (8) 1994 to present--interacted with the

Division of Federal Aid in FWS Region 3 to coordinate and distribute reports and renewals of federal aid contracts

b. NIO (1) 1994 to present--co-chaired and hosted FWS annual INAD meetings and (2) 1999 to present--contributed to the annual and midyear reports for the Project
c. SNARC: 1994 to present--contributed to the annual and midyear reports for the Project
d. UMESC (1) 1994 to present--summarized the data and prepared, coordinated, edited, and distributed the annual and midyear reports for the Project, (2) 1994 to present--prepared UMESC work plans, (3) established a website for Project information, (4) established an internal system to tract expenditure of funds and progress on studies at UMESC, and (5) 1994 to present--interacted with the Division of Federal Aid in FWS Region 3 to coordinate and distribute reports and renewals of federal aid contracts

4. Job No. 4: Assemble and submit NADA packages to CVM for approval
    a. National NADA Coordinator (1) 1994 to present--provided input on format for data package submissions, review and edit data packages before submission, (2) 1995--held a meeting under CVM sponsorship with 22 INAD coordinators of all INADs to increase coordination, communication, and consolidation of all INAD efforts and determine the general format of INAD/NADA submissions, (3) 1997--worked with UMESC to send separate DCI letters for chloramine-T, oxytetracycline, and formalin to accelerate the timetable for efficacy data submissions; reviewed data from DCIs
    b. NIO submitted technical section data packages on chloramine-T (target animal safety, efficacy) and oxytetracycline (efficacy)
    c. SNARC submitted technical section data packages on copper sulfate (environmental safety, human food safety, target animal safety, efficacy) and potassium permanganate (human food safety)
    d. UMESC (1) submitted technical section data packages for chloramine-T (environmental safety, human food safety, target animal safety, efficacy), formalin (target animal safety, efficacy), hydrogen peroxide (environmental safety, human food safety, target animal safety, efficacy), and oxytetracycline (human food safety, target animal safety, efficacy) and (2) 1997--sent separate DCI letters for chloramine- T, oxytetracycline, and formalin to accelerate the timetable for efficacy data submissions; reviewed data from DCIs and submitted reports to CVM; data accepted as supportive

e. Sponsors submitted technical section data packages on (1) AQUI-S™ (environmental summary), (2) chloramine-T (mammalian safety), (3) copper sulfate (product chemistry, mammalian safety), (4) formalin (supplemental NADAs), (5) florfenicol (product chemistry, mammalian safety, environmental safety, human food safety, target animal safety, efficacy), (6) hydrogen peroxide (product chemistry), (7) oxytetracycline (none), and (8) potassium permanganate (product chemistry)

5. Job No. 5: Address national aquaculture issues
    a. National NADA Coordinator (1) 1994 to present--presented status of aquaculture drug approvals to JSA Working Group on Quality Assurance in Aquaculture Production, (2) 1994 to present--provided liaison to NRSP-7 regarding drug developments in common, (3) 1996--prepared evaluation of the Animal Drug Availability Act of 1996 and how it affected Project drug approvals, (4) 1997 to present--is member of the Minor Use Minor Species (MUMS) Coalition that reviewed the various versions of the MUMS document and working with Congress on passing legislation, (5) 1999 to present--working with National Aquaculture Association and CVM to address antimicrobial resistance issues, (6) 1999--sent letter to CVM through the National Aquaculture Association to gain additional funding for CVM to alleviate backlogs in aquaculture drug reviews, (7) 2000 to present--co-chair with CVM for the Technical Subgroup for Drugs and Chemicals of the JSA Aquaculture Effluents Task Force; wrote the white paper that was submitted to EPA, and (8) 2000 to present--helped secure funds for the state of Iowa from the North Central Regional Aquaculture Center for pivotal efficacy studies on coolwater and warmwater species for florfenicol, oxytetracycline, and chloramine- T
    b. NIO presented status of its efforts on the Project to JSA Working Group on Quality Assurance in Aquaculture Production
    c. SNARC presented status of its efforts on the Project to JSA Working Group on Quality Assurance in Aquaculture Production
    d. UMESC (1) presented status of its efforts on the Project to JSA Working Group on Quality Assurance in Aquaculture Production, and (2) identified need for pivotal efficacy studies

D. Summary of accomplishments:

1. Identified, obtained, replaced, and retained committed company sponsors for all eight Project drugs after starting and finishing with only one drug (formalin) being covered by the original sponsors
2. Coordinated efforts that resulted in approved supplemental NADA for formalin to control fungi on the eggs of all fish and external protozoa and monogenetic trematodes on all fish
3. Coordinated efforts for 11 label claims for six drugs that are nearing completion toward approval
4. Identified alternate drugs and sponsors to replace sarafloxacin and benzocaine
5. Obtained new sponsors to replace sponsors for chloramine- T and oxytetracycline
6. Developed Cooperative Research and Development Agreements with company sponsors for AQUI-S™, copper sulfate, chloramine-T, and florfenicol
7. Identified data requirements for each of the eight Project drugs
8. Developed acceptable protocols for INADs and executing studies
9. Submitted numerous technical section data packages for all eight Project drugs
10. Had acceptance of numerous data submissions for anticipated new or supplemental NADA approvals
11. Established compassionate INAD program that has allowed widespread access to Project drugs while NADAs are being completed