NATIONAL COORDINATOR FOR AQUACULTURE
INADs/NADAs

Project Progress Report for the Period
July 15, 2004 to August 31, 2007

NCRAC FUNDING: $64,000 (July 15, 2004 to August 31, 2007)

PARTICIPANT:
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PROJECT OBJECTIVES
(1) Ensure effective communications among groups involved with Investigational New Animal Drug/New Animal Drug Applications (INADs/NADAs), including Canada.

(2) Serve as an information conduit between INAD/NADA applicants and the U.S. Food and Drug Administration's Center for Veterinary Medicine (CVM).

(3) Identify and encourage prospective INAD participants to become involved in specific investigational studies and NADA approval-related research.

(4) Seek the support and participation of pharmaceutical sponsors for INAD studies and NADAs and coordinate with INAD/NADA sponsors to achieve CVM approval more quickly.

(5) Guide prospective and current INAD holders on the format for INAD exemption requests and related submissions to CVM.

(6) Identify existing data and remaining data requirements for NADA approvals.

(7) Review, record, and provide information on the status of INADs and NADAs.

(8) Encourage and seek opportunities for consolidating the INAD/NADA applications.

(9) Coordinate educational efforts on aquaculture drugs as appropriate.

(10) Identify potential funding sources for INAD/NADA activities.

ANTICIPATED BENEFITS
Investigation and approval of safe therapeutic and production drugs for use by the aquaculture industry are some of the highest priorities currently facing the industry. At present, only a few approved compounds are available to the industry and further development of the aquaculture industry is severely constrained by a lack of approved drugs essential for treating more than 50 known aquaculture diseases. CVM has afforded the aquaculture industry

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1NCRAC has funded two NADA Coordinator projects. The termination report for the first project is contained in the 1999-00 Annual Progress Report. This progress report is for the second NADA Coordinator project. Ted R. Batterson serves as the facilitator for this project interacting with a steering committee in overseeing the Coordinator’s activities.
throughout the United States with a “window of opportunity” to seek approval of legal drugs to be used in their production practices. The need for additional drugs is great, but securing data necessary to satisfy the requirements of CVM for drug approval is time consuming, costly, and procedures are rigorous. The INAD/NADA process is the one method that allows the industry to provide CVM with data on efficacy and also aids producers in their production practices.

Coordination and educational efforts directed toward potential INAD/NADA applicants will save time and effort for both the industry and CVM. The National Coordinator for Aquaculture New Animal Drug Applications (National Aquaculture NADA Coordinator) serves as a conduit between an INAD/NADA applicant and CVM. The National Aquaculture NADA Coordinator helps to alleviate time demands on CVM staff, thus allowing more time to process a greater number of applications as well as increasing the breadth of research endeavors within the industry. The grouping of INAD applicants should help to alleviate redundancy, amalgamate efforts, and increase the amount of efficacy data, all of which should result in greater progress toward developing available, approved therapeutic and production drugs.

PROGRESS AND PRINCIPAL ACCOMPLISHMENTS
MAJOR APPROVALS

- Original NADA approval: 35% Perox-Aid® for the control of mortality due to (1) saprolegniasis on all finfish eggs, (2) bacterial gill disease on all freshwater-reared salmonids, and (3) external columnaris disease on all coolwater fish and channel catfish (approved January 11, 2007)

- Supplemental NADA approval: Aquaflor® for the control of mortality in all freshwater-reared salmonids due to coldwater disease (Approved March 19, 2007)

- Conditional approval: Aquaflor® for control of mortality in channel catfish due to columnaris disease associated with Flavobacterium columnare (Approved April 18, 2007)

- Abbreviated NADA approval: Tetroxy Aquatic® for marking in finfish fry and fingerlings (Approved April 20, 2007)

- Abbreviated NADA approval: Formacide-B® (generic copy of Parasite-S®, sponsored by Western Chemical, Inc.) for control of certain external parasites on finfish and shrimp and for the control of certain fungi on finfish eggs (Approved July 17, 2007)

CHLORAMINE-T (HALAMID®)—EXTERNAL ANTIBACTERIAL

Two initial label claims close to completion: (1) control of mortality due to (1) bacterial gill disease on all freshwater-reared salmonids and (2) external columnaris disease on walleye.

- On September 15, 2006, CVM granted Minor Use and Minor Species (MUMS) designation to Axcentive SARL, the sponsor of HALAMID®, for the following label claim for the control of mortality in freshwater-reared finfish (except freshwater-reared salmonids) due to bacterial gill disease.

- On April 13, 2007, the Upper Midwest Environmental Sciences Center (UMESC) submitted the final environmental assessment (EA) on chloramine-T to CVM.
In May 2007, CVM accepted GFI document #152 on microbial food safety for all finfish from Axcentive SARL.

On July 23, 2007, Axcentive SARL submitted to CVM a revised GFI document #159 on the safety of residues in human food for all fish for Halamid® (chloramine-T) prepared by the National Aquaculture NADA Coordinator with input from UMESC. The revision was based on the agency’s comments.

On October 11, 2007, UMESC received word that its final EA on Halamid® (chloramine-T) is acceptable to CVM.

CLOVE OIL (MAINLY EUGENOL)—ANESTHETIC
This drug is not currently under development for approval.

On April 24, 2007, CVM revised GFI #150 dealing with concerns related to the use of clove oil (eugenol) as an anesthetic for fish by correcting information on its ingredients and safety.

COPPER SULFATE (TRIANGLE BRAND COPPER SULFATE®)—EXTERNAL MICROBICIDE
One initial label claim close to completion: (1) control of mortality due to ichthyophthiriasis on channel catfish.

On October 30, 2006, CVM granted MUMS designation to Phelps Dodge Sales Company, the sponsor of Triangle Brand Copper Sulfate®, for the following label claim for the treatment of Ichthyophthirius multifilis on channel catfish cultured in earthen ponds.

In December 2006, the Stuttgart National Aquaculture Research Center submitted the final EA for earthen pond systems to CVM.

CVM reviewed the copper sulfate final EA for earthen pond systems and required additional changes.

ERYTHROMYCIN (AQUAMYCIN 100®)—ORAL ANTIBACTERIAL
One initial label claim close to completion: (1) control of mortality due to bacterial kidney disease in salmonids.

On October 2, 2006, the University of Idaho submitted to CVM the on the safety of residues in human food for all freshwater-reared salmonids (GFI #159).

On January 4, 2007, CVM granted MUMS designation to Bimeda, the sponsor of AQUAMYCIN 100®, for the control of mortality in freshwater-reared salmonids due to bacterial kidney disease associated with Renibacterium salmoninarum.

On January 11, 2007, CVM accepted as complete the GFI document #159 on the safety of residues in human food for all freshwater-reared salmonids from the University of Idaho. A right to reference proprietary toxicological data is needed to complete the Human Food Safety Technical Section.

On May 2007, the University of Idaho submitted the final EA to CVM.

FLORFENICOL (AQUAFLOR®)—ORAL ANTIBACTERIAL
Three supplemental label claims close to completion: Control of mortality due to (1) furunculosis in freshwater-reared salmonids, (2) systemic columnaris disease in freshwater-reared salmonids and catfish, and (3) Streptococcus iniae in hybrid striped bass and tilapia.

On March 19, 2007, CVM approved the Florfenicol (Aquaflor®) NADA from Schering-Plough Animal Health for control of mortality in all freshwater-reared salmonids due to coldwater disease.

On March 19, 2007, CVM accepted the effectiveness data as being complete from the Aquatic Animal Drug Approval
Partnership Program (AADAP) for control of mortality due to furunculosis in freshwater-reared salmonids.

- On April 18, 2007, CVM approved Aquaflor® for a conditional approval for control of mortality in channel catfish due to columnaris disease.

**FORMALIN—EXTERNAL MICROBICIDE**

One supplemental label claim close to completion: (1) control of mortality due to saprolegniasis on all freshwater-reared fish.

- On April 18, 2007, CVM approved Aquaflor® for a conditional approval for control of mortality in channel catfish due to columnaris disease.

- On July 17, 2007, an Abbreviated NADA (generic copy of Parasite-S®, sponsored by Western Chemical, Inc.) was granted by CVM for Formacid-B® (formalin) for control of certain external parasites on finfish and shrimp and for the control of certain fungi on finfish eggs. Formacid-B® is sponsored by B.L. Mitchell, Inc.

- The CVM Office of Research for the pivotal efficacy studies conducted by for the control of mortality due to saprolegniasis on channel catfish.

**HYDROGEN PEROXIDE—EXTERNAL MICROBICIDE**

One label claim in progress: (1) control of mortality on all warmwater finfish due to saprolegniasis.

- On September 6, 2006, CVM accepted the all other information technical section for three broad label claims from Eka Chemicals, Inc. in collaboration with the National Aquaculture NADA Coordinator.

- On November 9, 2006, CVM accepted the 35% PEROX-AID® labeling for three broad label claims from Eka Chemicals, Inc.

- On November 22, 2006, CVM accepted the Freedom of Information Summary for 35% PEROX-AID® for three broad label claims from Eka Chemicals, Inc.

- On November 30, 2006, Eka Chemicals, Inc. submitted the original NADA package for three broad label claims to CVM for approval.

- On January 11, 2007, CVM approved the 35% PEROX-AID® NADA for the control of mortality due to (1) saprolegniasis on all finfish eggs, (2) bacterial gill disease on all freshwater-reared salmonids, and (3) external columnaris disease on all coolwater fish and channel catfish.

- On May 2, 2007, CVM removed hydrogen peroxide from the list of Low Regulatory Priority aquaculture drugs because the drug is now the subject of an approved NADA for 35% PEROX-AID®. This means that 35% PEROX-AID® is the only hydrogen peroxide product that is legal to use.

- On November 30, 2006, Eka Chemicals, Inc. submitted the original NADA package for three broad label claims to CVM for approval.

- On January 11, 2007, CVM approved the 35% PEROX-AID® NADA for the control of mortality due to (1) saprolegniasis on all finfish eggs, (2) bacterial gill disease on all freshwater-reared salmonids, and (3) external columnaris disease on all coolwater fish and channel catfish.

**ISOEUGENOL (AQUI-S®)—ANESTHETIC**

One initial label claim in progress: (1) zero withdrawal anesthetic for sedation to handleable condition of all freshwater fish.

- On February 2004, the National Aquaculture NADA Coordinator obtained $60,000 in funding through the North Central Regional Aquaculture Center (NCRAC) for the radiolabeled material needed for the total residue depletion study on AQUI-S® to be conducted by the Upper Midwest Environmental Sciences Center (UMESC). The funds were provided to the sponsor, AQUI-S New Zealand LTD., so that the purchase of the
material did not have to go through the bidding process as would have been required for a federal agency. The material was purchased in the fall of 2004 and UMESC started the study in early 2005. UMESC completed the laboratory portion of the total residue depletion study on rainbow trout in the spring 2005.

UMESC submitted the final report to CVM on March 14, 2006. On January 31, 2007, UMESC submitted a response to CVM’s August 23, 2006 comments on the total residue depletion studies and a letter requesting the selection of the marker residue. The response was not definitive because of some concern of the radiochemical purity (95%) of the isoeugenol. CVM indicated that the agency cannot determine the significance of using test material with low radiochemical purity until the safe concentration for isoeugenol is calculated. CVM’s recommendation is intended to ensure that the reported total radioactivity in tissues is an accurate measurement of total residues. The total residue concentration is then related to the safe concentration determined by the acceptable daily intake (ADI). An ADI daily intake has not been assigned for isoeugenol because the toxicological requirements for isoeugenol have not been completed. This issue will not be resolved until the National Toxicology Program (NTP) has its meeting on isoeugenol toxicology studies in February 2008 and one more toxicology study is completed by the sponsor. If the safe concentration for isoeugenol is much lower than the reported total residues at the time point of concern (in this case 0-h for a zero hour withdrawal anesthetic), the issue of low radiochemical purity may be insignificant. If the safe concentration for isoeugenol is much higher than the reported total residues at the time point of concern, the low radiochemical purity of the test material may have to be addressed.

- On September 21, 2006, UMESC submitted a final report to Association of Fish and Wildlife Agencies on the development and validation of a determinative method to detect isoeugenol in fish tissues.
- On November 28, 2006, CVM accepted as complete from AADAP the effectiveness studies for all freshwater-reared finfish for sedation to handleable stage. Validation of the dose verification method is required before a technical section complete letter can be granted.
- On December 8, 2006, CVM accepted the target animal safety study protocol on rainbow trout from AADAP.
- On April 27, 2007, AADAP and UMESC announced they were suspending all research until the completion of the NTP review scheduled for February 2008 on studies conducted on mice and rats. The review had originally been scheduled for May 2007 but due to other priorities was delayed.
- The Gibbs method used to detect isoeugenol in efficacy and target animal safety studies was submitted by sponsor to CVM.

17α-METHYLTTESTOSTERONE (MT) —GENDER MANIPULATION AID
One initial label claim in progress: (1) masculinization of female early life-stage tilapia.

- Studies were initiated for effectiveness and target animal safety in late 2006 and early 2007.
- On July 30, 2007, interested parties met in Bozeman, Montana to discuss environmental assessment issues and to determine a course of action.
- On October 1, 2007, UMESC submitted to CVM the environmental safety studies and the water method for 17α-
methyltestosterone that were conducted and developed by the University of Wisconsin-Madison.

**METOMIDATE (AQUACALM®)—SEDATIVE**
One label claim in progress (1) sedative during transport of ornamental finfish.

- On November 13, 2006, CVM granted MUMS designation to Syndel Laboratories, LTD, the sponsor of AQUACALM®, for the following label claim for use as a sedative during transport of ornamental (non-food) finfish.

**OXYTETRACYCLINE DIHYDRATE (TERRAMYCIN® 200 FOR FISH)—ORAL ANTIBACTERIAL**
Three supplemental label claims close to completion: control of mortality due to (1) systemic columnaris disease in rainbow trout (*Oncorhynchus mykiss*) and (2) systemic coldwater disease in all freshwater-reared salmonids; (3) skeletal marking for salmonids.

- On August 15, 2006, CVM accepted GFI #159 for penaeid shrimp from the University of Arizona.
- On September 20, 2006, CVM accepted GFI #159 for the safety of residues in all freshwater-reared finfish in human food from Phibro Animal Health.
- On October 13, 2006, CVM requested a revision of the EA from UMESC.
- On March 15, 2007, CVM accepted GFI #152 for the microbial food safety for all freshwater-reared salmonids from AADAP.
- On April 13, 2007, UMESC submitted the amended EA to CVM.

**OXYTETRACYCLINE HYDROCHLORIDE (SEVERAL COMMERCIAL PRODUCTS)—MARKING AID**
- On July 23, 2007, Phibro Animal Health submitted to CVM a Labeling Technical Section to add the three new label claims and request the removal of the warning statement concerning use below 9.0°C (48.2°F).

**OXYTETRACYCLINE HYDROCHLORIDE (TERRAMYCIN-343®)—EXTERNAL ANTIBACTERIAL**
One label claim in progress: control of mortality in coolwater and warmwater finfish due to external columnaris disease.

- On April 20, 2007, CVM approved an abbreviated original (generic) NADA approval for TETROXY Aquatic® sponsored by Cross Vetpharm Group LTD. for use as a skeletal marking aid in finfish fry and fingerlings.

**POTASSIUM PERMANGANATE (CAIROX®)—EXTERNAL MICROBICIDE**
One label claim in progress: control of mortality in channel catfish due to external columnaris disease.

- On March 20, 2007, UMESC submitted to CVM efficacy studies on the control of mortality in coolwater and warmwater finfish due to external columnaris disease.
- On June 7, 2007, CVM granted MUMS designations to Pfizer Animal Health, sponsor of Terramycin-343®, for the following label claims: For the control of mortality in freshwater-reared finfish fry and fingerlings due to (1) external columnaris disease associated with *Flavobacterium columnare*, (2) bacterial gill disease associated with *Flavobacterium branchiophilum*, and (3) systemic columnaris disease associated with *Flavobacterium columnare*.

- On June 7, 2007, CVM granted MUMS designations to Pfizer Animal Health, sponsor of Terramycin-343®, for the following label claims: For the control of mortality in freshwater-reared finfish fry and fingerlings due to (1) external columnaris disease associated with *Flavobacterium columnare*, (2) bacterial gill disease associated with *Flavobacterium branchiophilum*, and (3) systemic columnaris disease associated with *Flavobacterium columnare*.

- On June 7, 2007, CVM granted MUMS designations to Pfizer Animal Health, sponsor of Terramycin-343®, for the following label claims: For the control of mortality in freshwater-reared finfish fry and fingerlings due to (1) external columnaris disease associated with *Flavobacterium columnare*, (2) bacterial gill disease associated with *Flavobacterium branchiophilum*, and (3) systemic columnaris disease associated with *Flavobacterium columnare*.
• On September 12, 2006, CVM granted MUMS designations to Carus Chemical Company, the sponsor of Cairox®, for the following label claims: For the control of mortality in (1) freshwater-reared finfish due to external columnaris disease associated with Flavobacterium columnare, (2) freshwater-reared salmonids due to bacterial gill disease associated with Flavobacterium branchiophilum, and (3) freshwater-reared salmonids due to coldwater disease associated with Flavobacterium psychrophilum.

SALMON GONADOTROPIN RELEASING HORMONE ANALOG (OVAPLANT®)—SPAWNING AID

One label claim under investigation: For the induction of spawning in ornamental fish

• On July 25, 2007, CVM granted MUMS designation to Syndel Laboratories, LTD, the sponsor of Ovaprim®, for the induction of spawning in ornamental fish.

GENERAL

• On July 18, 2007, the National Aquaculture NADA Coordinator gave an eight-hour presentation to the Veterinary Drugs Directorate (VDD) at its invitation. VDD is the Canadian equivalent of the U.S. CVM. The VDD was interested in (1) the successful aquaculture drug approval processes in the U.S., (2) our experience with various successful partnerships, and (3) insight into expediting the aquaculture drug approval processes in Canada.

• The designation provision of the MUMS Animal Health Act of 2004 gives sponsors seven years of marketing exclusivity. So far, the MUMS Office has granted 50 designations, 44 of those are to aquaculture drug sponsors who received extensive help from the National Coordinator for Aquaculture NADAs. The most recent MUMS designations are three for Pfizer Animal Health’s Terramycin 343® (oxytetracycline hydrochloride) on June 7, 2007 and one for Aquatic Life Sciences, Inc.’s Ovaplant® (salmon gonadotropin releasing hormone analog) on May 25, 2007. There have been three NADA approvals of MUMS designations for Eka Chemicals, Inc.’s 35% PEROX-AID® and two NADA approvals and one Conditional Approval of MUMS designations for Schering-Plough Animal Health’s AquafloR®.

• On May 4, 2007, CVM clarified the extra-label use of medicated feeds in minor species under the Compliance Policy Guide (#615.115) to include (1) veterinarian involvement, (2) treatment use only, (3) no production use, and (4) no feed reformulation or relabeling.

• From July to September 2007, the National Aquaculture NADA Coordinator gave presentations on innovations and status of aquaculture drug approvals at the 144th American Veterinary Medical Association Convention (Washington, D.C.), 13th Annual Drug Approval Coordination Workshop (Bozeman, Montana), Disease Management Strategies for the Aquatic Environment: Alternative and Innovations Symposium (San Francisco, California), and the Association of Fish and Wildlife Agencies, Drug Approval Working Group meetings (Louisville, Kentucky).

WORK PLANNED

The Work Plan is to continue meeting Objectives 1-8 and to help aquaculture drug sponsors develop major NADA documents and finalize their NADA submissions for approval.
**IMPACTS**

Establishment of the National Aquaculture NADA Coordinator position in May 1995 has resulted in coordination, consolidation, and increased involvement in the INAD/NADA process on 18 of the 19 high priority aquaculture drugs established in 1995 and activities on other new drugs of interest to aquaculture. INAD/NADA sponsors and other entities have initiated new INADs and made progress toward unified efforts on existing and new INADs/NADAs or have renewed their commitment to the INAD/NADA process on their drug products.

This enhanced coordination will help and has helped gain original approvals for new NADAs and extensions and expansions of approved NADAs. These include: (1) Original NADA approvals for human chorionic gonadotropin (Chorulon®), florfenicol (Aquaflor®), and hydrogen peroxide (35% PEROX-AID®); (2) Supplemental NADA approvals for florfenicol (Aquaflor®), formalin (Formalin-F®, Parasite-S®), oxytetracycline dihydrate (Terramycin® 200 for Fish), and oxytetracycline hydrochloride (OxyMarine®, Oxytetracycline HCL Soluble Powder-343®, Terramycin-343®); (3) Abbreviated NADA approvals for tricaine methanesulfonate (Tricaine-S®) and formalin (Formacide-B®); and (4) Conditional approval for florfenicol (Aquaflor®).

The approval of the candidate drugs will aid the aquaculture industry to reduce mortalities associated with infectious and handling diseases and to increase their efficiency by using spawning aids and gender manipulation aids. The domestic aquaculture industry will be better able to compete with foreign producers because there will be more legal drugs for producers to use.

**PUBLICATIONS, MANUSCRIPTS, PAPERS PRESENTED, AND REPORTS**

See the Appendix for a cumulative output for all NCRAC-funded National Aquaculture INAD/NADA Coordinator activities.

**SUPPORT**

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| TOTAL     | $64,000            |               | $99,936  | $215,077      | $92,900 | $407,913 | $471,913}
NATIONAL COORDINATOR FOR AQUACULTURE INADs/NADAs

Publications in Print


Papers Presented


Schnick, R.A. 1996. Status of aquaculture INADs and NADAs. Presenter and coordinator, Midcontinent Warmwater Fish Culture Workshop and INAD/NADA Coordination Meetings, Council Bluffs, Iowa, February 6-8, 1996.


Schnick, R.A. 1996. The procedures and responsibilities related to the amoxicillin INAD. Meeting of the Fish Growers of America, Memphis, Tennessee, October 2, 1996.


Schnick, R.A. 2005. Overview of the status of (1) Expansion and extension of the oxytetracycline (OTC) label claims, (2) Initial label claims for chloramine-T, (3) Microbial Food Safety submissions on these and other aquaculture drugs, and (4) Information on public and private aquaculture production statistics. Meeting on Microbial Food Safety Data Requirements for Oral Oxytetracycline and Chloramine-T for Approval in U.S. Commercial and Public Freshwater Aquaculture, Rockville, Maryland, October 5, 2005.


Schnick, R.A. 2006. Drug approval status: Why we are where we are and not where you thought we should be. 31st Eastern Fish Health Workshop, Charleston, South Carolina, March 27-31, 2006.


