Executive Summary of the Eighth Midyear Report of Progress

Performance Period: July 1, 2001 to December 31, 2001

Approval of Drugs for Public Fish Production

a project of the

International Association of Fish and Wildlife Agencies (IAFWA)

by

William H. Gingerich, Verdel K. Dawson, Guy R. Stehly, Jeffry A. Bernardy, Mark P. Gaikowski, Jeffery R. Meinertz, Jeffery J. Rach, Larry J. Schmidt, and Chu Vue

Upper Midwest Environmental Sciences Center
Biological Resources Division, U. S. Geological Survey, U.S. Department of the Interior
2630 Fanta Reed Road, La Crosse, Wisconsin 54603
Phone (608) 783-6451; Fax (608) 783-6066

Rosalie A. Schnick

National Coordinator for Aquaculture New Animal Drug Applications
Michigan State University
3039 Edgewater Lane, La Crosse, Wisconsin 54603-1088
Phone (608) 781-2205; Fax (608) 783-3507

Bill R. Griffin

Harry K. Dupree Stuttgart National Aquaculture Research Center
Agricultural Research Service, U.S. Department of Agriculture
P.O. Box 860, Stuttgart, Arkansas 72160-0860
Phone (870) 673-4483; Fax (870) 673-7710

David Erdahl, James Bowker, and Dan Carty

Bozeman National INAD Office, Fish Technology Center
U.S. Fish and Wildlife Service
4050 Bridger Canyon Road, Bozeman, Montana 59715
Phone (406) 587-9265; Fax (406) 582-0242

Table of Contents

Executive Summary

The International Association of Fish and Wildlife Agencies Project (IAFWA Project) entitled "Federal-State Aquaculture Drug Approval Partnership Project" has now completed seven years and is midway through its eighth and final year. New Animal Drug Application (NADA) submissions to the Center for Veterinary Medicine (CVM) to support original or supplemental approvals for IAFWA Project drugs are the result of efforts by the Upper Midwest Environmental Sciences Center (UMESC), Harry K. Dupree Stuttgart National Aquaculture Research Center (HKD-SNARC), U.S. Fish and Wildlife Service (FWS) Bozeman National Investigational New Animal Drug (INAD) Office (NIO), other public agencies such as state natural resources agencies, the private aquaculture sector, sponsors, and the National Coordinator for Aquaculture NADAs.

PROJECT SUCCESSES - Successes for the IAFWA Project are the (1) identification and retention of committed sponsors for all IAFWA Project drugs, (2) identification of alternate drugs and sponsors to replace sarafloxacin and benzocaine, (3) identification of data requirements for each drug, (4) execution of studies according to acceptable protocols, (5) submissions of technical sections to CVM by its partners mentioned above, and (6) acceptance of these technical section submissions by CVM that should lead to new or supplemental NADA approvals. Currently, all eight IAFWA Project drugs have pharmaceutical or chemical company sponsors, in contrast to only three when the IAFWA Project began in 1994. A first major and tangible success was the broad supplemental NADA approval in 1998 for formalin to control certain fungi on the eggs of all fish and certain external protozoa and monogenetic trematodes on all fish. Other broad approvals are expected for hydrogen peroxide and oxytetracycline (OTC). Limited approvals are expected for AQUI-S? , chloramine-T, copper sulfate, and florfenicol and potassium permanganate.

YEAR 8 MIDYEAR HIGHLIGHTS

AQUI-S™

A multi-state conservation grant proposal was funded to allow UMESC to develop critical human food safety data for a representative coldwater fish, the rainbow trout. A contract has been let to synthesize the radiolabeled test article and the material is expected to be delivered to UMESC in early March, 2002. Protocols have been developed and submitted for review by CVM for critical total residue depletion studies.

Chloramine-T

All holders of chloramine-T INADs were sent notices in March 2001 that CVM has concerns for the possible mammalian safety of p-TSA, the marker residue of chloramine-T and will not renew slaughter authorizations (including release of fish) after a certain point (depends upon the date of INAD renewal). This policy will continue until CVM receives new information from the sponsor that addresses CVM's mammalian safety concerns for p-TSA. The sponsor met with CVM on October 31, 2001 to resolve the remaining issues and determine a course of action that the company is currently pursuing.

A data package to address the human food safety technical section is nearing completion to allow for a broad approval for many or most of the cold, cool, and warm water fish species important to public aquaculture. UMESC submitted two major study completion reports to support the determinative method for p-TSA in all fish species and a third report to document marker residue depletion of p-TSA in rainbow trout. The submission of two additional major maker residue depletion studies, one for a representative cool water species and one for a representative scaled warm water species with complete the entire data package for the determinative method. The initial submissions should be complete by March, 2002. UMESC continues to work with the Office of Research, CVM to develop the appropriate confirmatory method for the marker residue p-toluene-sulfonamide in a broad number of cold, cool and warm water fish.

A data package to address the target animal safety technical section for a broad range of cool and warm water fish species important to public aquaculture is nearing completion. The target submission date of this comprehensive target animal safety study package to CVM is March, 2002.

A comprehensive environmental summary for the broad use of chloramine-T in public aquaculture is nearing completion. The target submission date to CVM is March, 2002.

UMESC successfully obtained funding to develop a reproducible disease model for external columnaris in a variety of cultured fish species through the Multi-State Conservation Grant process.

Hydrogen Peroxide

CVM accepted as complete the target animal safety technical section for hydrogen peroxide use on all finfish on October 4, 2001.

UMESC has continued to expand its coordination and collaboration to develop additional efficacy data in support of the use of hydrogen peroxide by initiating three compassionate INADs. Participation in the three INAD protocols has increased immensely over the past year from 24 INAD units in 2000 to 115 units in 2001.

UMESC submitted five study reports on hydrogen peroxide efficacy to control mortality from saprolegniasis on a variety of fish eggs.

UMESC successfully obtained funding to develop a reproducible disease model for external columnaris in a variety of cultured fish species through the Multi-State Conservation Grant process.

Negotiations and Contract Coordination

A bill originally entitled "Minor Animal Species Health and Welfare Act of 2000" was introduced in the U.S. Congress in 2000. The Act will facilitate and accelerate the approvals of aquaculture drugs. A revised bill “Minor Use Minor Species Animal Health Act of 2001 was reintroduced into the House on May 24, 2001 (HR-1956) and into the Senate on August 2, 2001

(S-1346). Efforts are being made to add this bill to another piece of legislation to get it passed.

In January 2001, EPA indicated that the agency would not consider any drugs or chemicals to be pollutants of concern for regulating effluents from hatcheries. Instead, EPA will ask that drugs and chemicals be part of good management practices.

Nine pharmaceutical and chemical companies met with aquaculture interests in August 2001 to indicate their potential or actual interest in sponsoring their products for aquaculture approval in the United States.

On December 28, 2001, the National Aquaculture NADA Coordinator sent a request to all 50 state fish chiefs to gather annual state fish production data that will be of interest to potential and actual pharmaceutical and chemical sponsors.

On December 27, 2001, the National Aquaculture NADA Coordinator sent a request to 30 state fish chiefs that are recently or currently involved in the Federal-State Aquaculture Drug Approval Partnership Program to determine their state's unmet label claim needs when the project ends.

UMESC was awarded three contracts by the International Association of Fish and Wildlife Agencies as part of the Multi-State Conservation Grant process and a fourth proposal by Arkansas State University in collaboration with the HKD-SNARC was also funded.

An interagency agreement with the Office of Research, CVM, to develop a confirmatory method of p-TSA in tissues of a variety of cultured freshwater fish continues. The Gas Chromatography/Mass Spectrometry method has been developed. The method is being tested for several cold, cool and warm water fish species.

Oxytetracycline

UMESC obtained funding to develop data to support an immersion NADA for OTC in certain fish species through the Multi-State Conservation Grant Program.

UMESC submitted correspondence and additional data concerning a CVM review of the analytical method for oxytetracycline in fish tissue on October 5, 2001 that should allow the method to be accepted for a wide variety of fish.

Potassium Permanganate

Arkansas State University in collaboration with the Harry K. Dupree Stuttgart National Aquaculture Research Center were successful in obtaining funding to develop appropriate data to support an environmental assessment of potassium permanganate in pond culture.

DRUG STATUS

Certain label claims are nearing completion (see Tables 1 and 2 for details):

Chloramine-T--mortality from bacterial gill disease on salmonids reared in freshwater
Copper sulfate--*Ichthyophthirius* on catfish in earthen ponds
Florfenicol -- mortality from furunculosis in salmonids (submitted by the sponsor)
Florfenicol - - mortality from enteric septicemia in channel catfish (to be submitted by sponsor)
Formalin--mortality from saprolegniasis on all fish
Hydrogen peroxide--mortality from saprolegniasis on all fish eggs
Hydrogen peroxide--mortality from saprolegniasis on all fish
Hydrogen peroxide--mortality from bacterial gill disease on salmonids reared in freshwater
Oxytetracycline--mortality from systemic columnaris disease in all salmonids
Oxytetracycline--mortality from systemic coldwater disease in all salmonids
Oxytetracycline--otolith marking of all fish by immersion (submitted by the National ResearchSupport Project Number 7)

All the technical sections (except efficacy) for which the IAFWA Project is responsible are expected to have been submitted to the Center for Veterinary Medicine by September 2002 to allow for broader label claims when efficacy data are generated beyond 2002 for chloramine-T, formalin, hydrogen peroxide, and oxytetracycline (see Table 1 for details). The sponsor of florfenicol is completing the technical sections on florfenicol for salmonids and catfish but the Drug Approval Working Group decided not to allow IAFWA Project funds to be expended to extend the label claims to cool and scaled warm water fish. Amendments to broaden initial or existing aquaculture drug approvals will be possible after pivotal and supporting efficacy data are generated and accepted to substantiate label claims beyond those mentioned above (see Tables 2 and 3 for details). At the present time, adequate efficacy data exist mainly for salmonids but are lacking for cool water and warm water fish (see Table 3 for details). The lack of efficacy data jeopardizes the addition of these species or disease indications to label claims in original or amended NADAs.

New INADs are now in place at NIO to develop efficacy data on florfenicol and AQUI-S? , and Cooperative Research and Development Agreements are also in place with the sponsors for AQUI-S? , copper sulfate, chloramine-T and florfenicol. In the latter half of 2000, new sponsors replaced the original sponsors for chloramine-T and oxytetracycline.

Details of all items in this executive summary can be found in the complete text of the Eighth Midyear Report of Progress located on the UMESC website at http://www.umesc.er.usgs.gov.

CHALLENGES - Although the IAFWA Project is producing successes for the development of drugs for public aquaculture, three major factors have hampered efforts to gain broad approvals for all IAFWA Project drugs: (1) loss of drugs from the IAFWA Project, (2) lack of successful efforts to generate required data to demonstrate effectiveness, especially for cool and warm water fish, (3) additional requirements for original or revised environmental assessments, and (4) potential additional requirements for chloramine-T mammalian safety studies . The loss of drugs from the IAFWA Project has been addressed with the substitution of florfenicol and AQUI-S? . Based on the remaining challenges, the following issues and action items are presented here:

ISSUES AND ACTION ITEMS:

1. **Efficacy Issues --** There are three efficacy issues that must be addressed. These include: (a)

Label claims for cool and warm water fish cannot be added to many original or amended NADAs because efficacy data are lacking; (b) Continued existence of INADs after IAFWA Project completion is uncertain because INAD holders need to show progress toward approval for remaining label claims or the INAD will be cancelled by CVM; (c) Use of drugs beyond that allowed in approved NADAs (i.e., Extra-Label Use) will be difficult or impossible because certain limitations will restrict their use. These are: (1) a valid veterinarian-client-patient relationship is required, (2) a drug used beyond that allowed on its label must be an approved animal or human drug in the approved formulation and obtained from the legitimate sponsor; (3) Use of an alternative approved drug is possible only if the drug approved for that disease does not work, and (4) Extra-Label Use is very limited for medicated feed applications in aquaculture because no "top coating" of feed with a drug is allowed and producers can use only oxytetracycline and Romet-30 trout and catfish medicated feeds at the present time.

Alternative Actions:

?? Accelerate involvement of states to generate efficacy data through existing INADs;

?? Determine from CVM what INADs can continue if no progress is being made to complete the efficacy requirements for certain label claims;

?? Leave efficacy effort as is and rely on limited Extra Label Use to cover the species and diseases not on the approved label and risk that a number of fish species will go untreated and be lost to production.

Priority Recommendations for Efficacy Studies

The IAFWA Drug Approval Working Group needs both to prioritize drugs and their label claims to facilitate development of efficacy data for broad approvals. Possibilities for these priorities are found mainly in the red blocks of Table 2. Project coordinators are making the following recommendations in priority order based on the likelihood of the successful completion of all other technical sections except efficacy for the following label claims:

1. Hydrogen peroxide - Supporting efficacy data for saprolegniasis on cool and warm water fish
2. Hydrogen peroxide - Additional supporting efficacy data for saprolegniasis on cool and warm water fish eggs
3. Hydrogen peroxide - Pivotal and supporting efficacy data for bacterial gill disease on cool and warm water fish
4. Hydrogen peroxide - Pivotal and additional supporting efficacy data for external columnaris disease on all fish
5. Hydrogen peroxide - Pivotal efficacy data for external parasites on all fish
6. Oxytetracycline - Pivotal and supporting efficacy data for systemic columnaris disease in cool and warm water fish

7. Oxytetracycline – Pivotal efficacy data for *Aeromonas* sp. in cool water fish
8. Chloramine-T – Pivotal and supporting efficacy data for external columnaris disease on all fish

2. **Environmental Safety Issues** – Additional environmental safety studies may be required by CVM for AQUI-S? , chloramine-T, hydrogen peroxide and oxytetracycline.

Alternative Actions:

?? Continue the Multi-State Conservation Grant Program with aquaculture drug approvals as one of the major needs beyond 2002.

?? Identify other funding sources to include company sponsors and other granting sources.

3. **Chloramine-T Mammalian Safety Issues** --Additional mammalian safety studies on chloramine-T may be required by CVM if the sponsor cannot resolve the issues or fund the additional required studies.

Alternative Actions:

?? Identify funding sources from outside of IAFWA Project to fund mammalian safety studies required by CVM (possible sources include FWS, private aquaculture sector, other granting sources);

?? If adequate outside funding sources cannot be identified, stop work on chloramine-T;

?? Stop work on other IAFWA Project drugs and redirect funds to required mammalian safety studies.

Table 1. Status of technical sections (except efficacy) for "all fish" label claims

Project Drug	Product Chemistry	Mammalian Safety	Environmental Safety			Human Food Safety			Target Animal Safety		
	All Fish	All Fish	Cold	Cool	Warm	Cold	Cool	Warm	Cold	Cool	Warm
AQUI-S?											
Chloramine-T											
Copper sulfate (eggs)						NA	NA	NA			
Copper sulfate (fish)											
Formalin (eggs)											
Formalin (fish)											
Hydrogen peroxide (eggs)											
Hydrogen peroxide (fish)											
Oxytetracycline											
Potassium permanganate (eggs)						NA	NA	NA			
Potassium permanganate (fish)											

Legend

	Work required but not begun
	Data collection underway
	Data submitted to CVM
	Data accepted by CVM
	Prior or amended approval
	Not applicable

Table 2. Status of efficacy technical sections for "all fish" label claims

Project Drug	Disease Indication	Fish Group [1]					
		Cold water fish		Cool water fish		Warm water fish	
		Pivotal	Supporting	Pivotal	Supporting	Pivotal	Supporting
AQUI-S?	Anesthetic						
Chloramine-T	Bacterial gill disease						
	External columnaris disease						
Copper sulfate	Saprolegniasis - eggs						
	Saprolegniasis - fish						
	External columnaris disease						
	Ichthyophthirius						
	Other external parasites						
Florfenicol	Furunculosis			NA	NA	NA	NA
	Systemic columnaris disease						
	Coldwater disease			NA	NA	NA	NA
Formalin	Saprolegniasis - eggs						
	Saprolegniasis - fish						
	External parasites						
Hydrogen peroxide	Saprolegniasis - eggs						
	Saprolegniasis - fish						
	Bacterial gill disease						
	External columnaris disease						
	External parasites						
Oxytetracycline	Systemic columnaris disease						
	Systemic coldwater disease			NA	NA	NA	NA
	Aeromonas sp.						
	Marking otoliths						
Potassium permanganate	Saprolegniasis - eggs						
	Saprolegniasis - fish						
	External columnaris disease						
	Ichthyophthirius						
	Other external parasites						

	Work required but not begun		Data accepted by CVM
	Data collection underway		Prior or expanded approval
	Data submitted to CVM	NA	Not applicable

[1] Designations may represent one or more species within a fish group

Table 3. Efficacy data needed for "all fish" label claims

Drug (lead facility)	Disease	Study Type	Fish Group
Chloramine-T (NIO)	Bacterial gill disease	Pivotal/ Supporting	Cool and warm water fish
	External columnaris disease	Pivotal/Supporting	All fish
Copper sulfate (HKD-SNARC)	Saprolegniasis on fish eggs	Supporting	Warm water fish eggs
	Saprolegniasis on fish eggs	Pivotal/Supporting	Cool and cold water fish eggs
	Saprolegniasis on fish	Pivotal/Supporting	All fish
	External columnaris disease	Pivotal/Supporting	All fish
	External parasites (except *Ichthyophthirius*)	Pivotal/Supporting	All fish
Hydrogen peroxide (UMESC)	Saprolegniasis on fish eggs	Pivotal/Supporting	Cool and warm water fish eggs
	Saprolegniasis on fish	Supporting	All fish
	Bacterial gill disease	Pivotal/Supporting	Cool- and warm water fish
	External columnaris disease	Pivotal/Supporting	All fish
	External parasites	Pivotal/Supporting	All fish
Oxytetracycline (NIO)	Systemic columnaris disease	Pivotal/Supporting	Cool and warm water fish
	Systemic cold water and columnaris diseases	Supporting	Additional salmonids
	Aeromonas sp.	Pivotal	Cool water fish
Potassium permanganate (HKD-SNARC)	Saprolegniasis on fish eggs	Pivotal/Supporting	All fish eggs
	External columnaris disease	Pivotal/Supporting	All fish
	Ichthyophthirius	Pivotal/Supporting	Cool and cold water fish
	Ichthyophthirius	Supporting	Warm water fish
	External parasites (except *Ichthyophthirius*)	Pivotal/Supporting	All fish

Legend:

	HKD-SNARC=Harry K. Dupree Stuttgart National Aquaculture Research Center
	NIO=U.S. Fish and Wildlife Service National INAD Office
	UMESC=Upper Midwest Environmental Sciences Center