

## **Progress Report : Approval of Drugs for Public Fish Production**

a project of the

### **International Association of Fish and Wildlife Agencies (IAFWA)**

May 1996

#### **INTRODUCTION:**

This progress report is intended as an information source for partners in the joint Federal-State Aquaculture Drug Registration Partnership. We have been informed that much of the progress made during the first portion of this project has not been transferred to the "user" level. We encourage interchange of ideas and suggestions for improvements in order to better coordinate our efforts to obtain the drug approvals that we seek from this project. This initial faxed message to our cooperators is a means of periodically communicating major developments under this project. We intend to send these reports out in April and November each year. These dates will complement the midyear and annual formal reporting dates of January and August. As events warrant, we will also use this forum to distribute important information or report on important events.

#### **CURRENT ISSUES:**

Several issues were raised during discussions at the session on Investigational New Animal Drug (INAD) -New Animal Drug Applications (NADA) coordination at the Warm Water Fish Culture Workshop in Council Bluffs, IA on February 7-8, 1996. The topics relate to efforts to define requirements for facilities volunteering to conduct pivotal studies to generate efficacy data to support label claims for chloramine-T. Although these requirements are identified for chloramine-T, they will apply to efficacy studies on other aquaculture therapeutants.

- **Pivotal Study Site Requirements for Efficacy Trials for Chloramine-T:** For facilities that wish to serve as pivotal study sites for generation of efficacy data for chloramine-T, the following requirements must be met.
  - Studies must have separate protocols for each disease indication, independent of the original INAD protocol, that identify **specific courses of therapy**. Each protocol must include appropriate positive and negative controls and define specific methods to evaluate the treatment so that efficacy can be demonstrated statistically.
  - Each **study** at a pivotal study site must comprise a minimum of three separate trials (or runs); **each trial must represent a distinct epizootic from a single causative disease agent**.
  - The causative agent of the disease must be **unambiguously identified** using accepted and established methods of diagnosis.
  - Provisions must be made to verify the treatment concentrations associated with the therapy through **accepted** analytical methods.
  - **All pivotal studies** must be conducted in accordance with **provisions similar to Good Laboratory Practices (GLP)** for protocol compliance, data acquisition, data storage/security, and record keeping.

- **Minimum Requirements to Place Fish Species or Families on a Label for Disease Treatment with Chloramine-T**
  - **Pivotal studies** will be required **at a minimum** in a major representative species from each of the five major families cultured in public aquaculture (i.e. Salmonidae, Ictaluridae, Esocidae, Percidae, Centrarchidae, and perhaps Serranidae) if any members of that family group are to be considered on the label.
  - **A separate pivotal study** will be required for each major representative fish species **for each disease indication** and for each type of use (**i.e. therapeutic vs. prophylactic treatments**).
  - **To place a fish family on the label, at least one additional species in that family should also be tested** other than the species used for the pivotal study. That is, for the family Salmonidae to be on a label, there must be a pivotal study in one major representative species, and a “**non-pivotal**” (but scientifically sound) study conducted on at least one additional salmonid species.

**Note: CVM has indicated that all other species not tested, or for which only minimal work has been done, would be covered by the label under a disclaimer. It is unclear to us at this point how many pivotal studies will be required by CVM. This issue will be clarified before the November workshop mentioned below.**

- **INAD/NADA Coordination Meeting for Chloramine-T Pivotal Study Sites:** Leroy Heman has consented to host a coordination meeting of chloramine-T INAD holders in Kansas City, MO in early November, 1996. Tentative dates for the workshop are November 7 all day and the morning of November 8. The purpose of the meeting will be to identify pivotal study sites for chloramine-T for both bacterial gill disease and flexibacteriosis in the five major families listed above, to develop unified protocols for the efficacy trials, and to ensure that GLP support is coordinated for the selected study sites. This meeting is extremely important. Achieving a drug approval for chloramine-T is linked to our success in conducting successful pivotal study efficacy field trials. Those individuals participating in the chloramine-T INAD's, particularly the INAD coordinators, should plan on attending this workshop. Confirmation of the exact dates, times, and location for the workshop will be forthcoming.

#### **HIGHLIGHTS OF PROGRESS: (January 1, 1996 to May 15, 1996)**

- **Benzocaine** (anesthetic): 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, Center for Veterinary Medicine (CVM), U. S. Food and Drug Administration (FDA). This 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 tissue with time after exposure.
- **Chloramine-T** (external antibacterial): 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 CVM to declare para-toluene sulfonamide as a marker residue for chloramine-T in juvenile rainbow trout. Development of a regulatory method for chloramine-T residues can now go forward.

- **Copper Sulfate** (microbiocide): A study to determine the accumulation of copper in channel catfish exposed to copper sulfate was completed and submitted to CVM. This data indicate 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. Negotiations are underway with the University of Mississippi to complete an environmental assessment of use of copper sulfate in aquaculture.
- **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. A study protocol for developing analytical methods for sarafloxacin in fish plasma and edible tissue has been approved and initial experiments have been conducted at the Upper Mississippi Science Center (UMSC). Sarafloxacin is the oral model compound for the development of Crop Grouping information.
- **Formalin** (microbiocide): 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. This data will support the extension of the current formalin label as a fungicide to include the eggs of warmwater and other coolwater species.
- **Hydrogen Peroxide**: (microbiocide) A target animal safety study on the toxicity of hydrogen peroxide to representative warm- and coolwater fish eggs is in progress. A report was submitted to CVM requesting an amendment to the current low regulatory priority ruling on hydrogen peroxide as a fungicide to allow its use at concentrations up to 1,000  $\mu\text{L/L}$  (ppm) on fish eggs.
- **Negotiations and Contract Coordination**: INAD/NADA coordination meetings were held in Rockville, Maryland on November 1-2, 1995 and at the Warm Water Fish Culture Workshop in Council Bluffs, Iowa on February 6-8, 1996. Items discussed in the meetings included ways to consolidate INADs of participating states and coordination of resources for consolidated submission of data to support efficacy label claims and coordination of efforts to identify and support pivotal study sites for developing efficacy data.
- **Negotiations and Contract Coordination**: The Aquaculture Committee of the IAFWA was provided with reports on progress to date, the projected work plan for year 3, and budgets for the Approval of Drugs for Public Fish Production Project at the 61st North American Conference on Wildlife and Natural Resources, March 24, 1996, Tulsa, Oklahoma. The Aquaculture Committee reviewed and accepted the projected research study objectives along with the budget. The Committee was interested in how to add more states to the project and whether the budget shortfall would adversely impact the completion of the project's 5-year objectives. It was estimated that an additional \$1.8 million and two years would be needed to complete all of the original objectives. The Committee discussed ways to provide the needed money and time.
- **Negotiations and Contract Coordination**: An Interagency Agreement (IAG) has been developed with CVM's Office of Science to coordinate contracted studies to fulfill data requirements for chloramine-T and benzocaine.
- **Negotiations and Contract Coordination**: Negotiations and discussions with Eka Nobel Inc. resulted in the company submitting a letter of intent to CVM to pursue a INAD/NADA on hydrogen peroxide. CVM granted their request on January 19, 1996.
- **Negotiations and Contract Coordination**: Based on progress made by the Approval of Drugs for Public Fish Production Project, CVM Director Dr. Steven Sundlof, announced on February 15, 1996 at "Aquaculture '96" that CVM anticipates near-term approvals of copper sulfate as a microbiocide for all fish, formalin as a microbiocide for all fish and fish eggs, and oxytetracycline as a marking agent

for all fish. He listed several other project drugs for potential or anticipated NADA approvals by the year 2000: chloramine-T for control of bacterial gill disease and flexibacteriosis for all fish, hydrogen peroxide as a fungicide for all fish, oxytetracycline as an antibacterial for shrimp and all fish, potassium permanganate as a microbiocide for all fish, and sarafloxacin to control enteric septicemia in catfish.

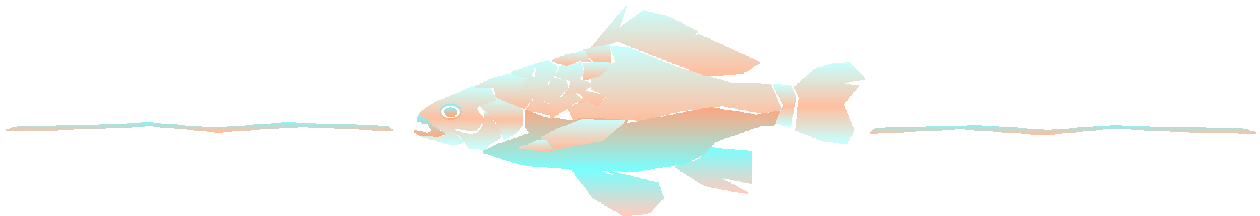
- **Oxytetracycline** (antibacterial, marking agent): Discussions with CVM determined a need for a bridging study of the High performance Liquid Chromatography (HPLC) method used with the official microbiological method, before residue depletion studies are completed for extension and expansion of the label. An HPLC method for the determination of oxytetracycline in the fillet of salmon was adapted for use with several species of fish and is under evaluation. Arrangements are being made to conduct the bridging study this summer.
- **Potassium Permanganate** (Microbicide): A study of the accumulation of manganese in the edible muscle of channel catfish (*Ictalurus punctatus*) following exposure to water borne potassium permanganate is in progress. This study will address the human food safety data requirements for potassium permanganate in channel catfish tissue. A literature review for an environmental assessment of the use of potassium permanganate in aquaculture has begun.

Your questions and comments to the information provided within this report, as well as the organization of the report itself, are encouraged. This project is designed to help public aquaculture develop urgently needed medicinal therapeutants and anesthetics. It is your project! If you have information to share or additional questions after reading this first release, please contact us. We will do our best to provide you with the information you are seeking. If we are unable to answer your questions directly, we will make every effort to put you in contact with those who are best qualified to address your concerns. The following individuals have contributed to the information in this progress update and may be contacted directly for further clarification of topic areas.

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