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Investigational New Animal Drug (INAD) Exemptions and the National INAD Program (NIP)

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The United States Food and Drug Administration (FDA) defines a drug as an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and an article (other than food) "intended to affect the structure or any function of the body of man or other animals." Because of this broad definition, even compounds such as salt and ice are considered drugs. Before 1994, the FDA chose not to regulate the use of drugs for minor species. This allowed aquaculture producers to use virtually anything available to treat their fish, and there were few efforts to gain aquaculture drug approvals. In 1994, however, the FDA began regulating the use of drugs in minor species, which left aquaculture producers with a bare bones medicine chest of only three approved aquaculture drugs.

New aquaculture drug approvals are rare. Drug sponsors have reported that it can cost $10 million to $20 million and take 10 to 15 years to gain approval for a new drug, and there is little economic incentive to do so. For a drug to be approved it must be demonstrated that the drug is efficacious, safe (to the target animals, humans, and environment), manufactured consistently without impurities, and stable. On a positive note, the FDA has recently approved the use of Aquaflor® (florfenicol), Terramycin® 200 for Fish (oxytetracycline), and 35% PEROX-AID® (hydrogen peroxide). These new drugs provide both public and private sector aquaculture programs with critical new management tools and highlight the success of the U.S. Fish and Wildlife Service's Aquatic Animal Drug Approval Partnership Program.

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The acronym INAD stands for Investigational New Animal Drug. An INAD exemption is a process by which the FDA authorizes and controls the transport, possession and use of unapproved drugs. The National INAD Program (NIP) for aquatic animals is administered by the U.S. Fish and Wildlife Service's (FWS) Aquatic Animal Drug Approval Partnership Program (AADAP), which began in 2003 and is located in Bozeman, Montana. The NIP provides the means through which public and private agencies or organizations (cooperators) are granted exemptions to use certain critical but unapproved drugs necessary to maintain the health and fitness of aquatic species. INAD exemptions are granted by the FDA and are a critical tool fisheries managers and aquaculturists can use to meet management objectives. INAD exemptions also contribute important drug efficacy and safety data that are used to support the future approval of new drugs. The FDA expects that information generated will be used to support a New Animal Drug Approval (NADA). INAD exemptions are not to be considered "use permits."

INAD procedures and use

The NIP is operated on a cost-reimbursable basis with all non-federal facilities paying $400 for each INAD exemption per facility per year. The money collected helps fund the operational needs of the NIP. All participating agencies/organizations must sign a cooperative agreement with the FWS. This agreement establishes the obligations to be met and the procedures to be followed by the FWS and the cooperators in allowing the use of specific drugs and chemicals.

The INAD process typically involves a drug manufacturer, an investigator, a study monitor, a sponsor, a study director, and a field trial coordinator. The drug manufacturer is the company making and/or providing the drug; the investigator is a designated person at the facility desiring to obtain and use the INAD exemption; the study monitor can be an FWS employee or an employee of the facility; and the sponsor, study director, and field trial coordinator are all FWS employees involved in monitoring and administering the INAD project. The investigator or a person under his/her direct supervision is responsible for implementing the INAD study protocol, making observations, collecting samples, and recording and reporting data during the field trials. The study monitor is responsible for reviewing the study protocol, drug use, and data reporting forms from the investigator that are submitted to the field trial coordinator. The field trial coordinator analyzes and summarizes the data and prepares an annual report that is submitted to the FDA.

Although the specific requirements for each INAD may vary depending on the drug being used and the requirements for data collection, fish disposition, drug disposition etc., in general an investigator will complete a current year sign-up and information sheet; worksheet for designing individual field trials; and a report on the receipt of the drug, drug inventory, and results. Following is a brief description of each type of form:

1. To enroll in the NIP the investigator or study monitor fills out the current year sign-up and information sheet. This form includes the investigator's and study monitor's contact information and shows which INADs (drugs) the facility is interested in using and on what fish species.
2. The worksheet for designing individual field trials includes the address of the facility, the number and size of fish to be treated, the drug dosage and method of delivery, and a description of the study design (a detailed description of the purpose of the clinical trial). This form must be signed by both the investigator and study monitor and sent to the field trial coordinator before the drug is used.
3. The report on the receipt of the drug must be completed by the investigator immediately upon receipt of the drug. The study monitor should send a copy of the form, signed by both the investigator and monitor, to the field trial coordinator within 10 days of receiving the drug.
4. The investigator should initiate a new drug inventory form upon receipt of each shipment of the drug and update it whenever the drug is used, transferred or discarded. The investigator should save all copies of this form until the end of the calendar year, at which time he/she should file all originals and send copies to the study monitor, who should check the form for accuracy and send a copy signed by the investigator and study monitor to the AADAP Office for inclusion in the permanent file.
5. The results report form collects information on the actual INAD treatment (how many fish were used, the efficacy of the drug, safety information, withdrawal period, etc.). It is submitted to the study monitor within 10 days of completion of the study. The study monitor reviews the results report form for accuracy and sends it to the field trial coordinator. The field trial coordinator reviews all INAD forms for accuracy and submits a summarized report to the FDA for each completed INAD study.

Specific requirements and associated forms for each INAD exemption can be found at the AADAP website (*http://www.fws.gov/fisheries/aadap/home.htm*).

The AADAP office is in the process of developing an automated website that would allow data to be reported online and collected in a large database. It is hoped that the new online reporting system will be less labor intensive as well as more accurate and complete. The new system will be tested with a few facilities/agencies to ensure that it is fully functional. Assuming that the new system is successful, it should become mandatory for INAD reporting in the future.

Currently available INADs

A list of INAD exemptions available as of Fall 2011—with their intended uses and sources—is shown in Table 1. More information on available INAD exemptions can be found at the AADAP website (*http://www.fws.gov/fisheries/aadap/home.htm*).

Goals of the NIP and AADAP

The goal of the NIP is to give aquaculture researchers and producers access to unapproved drugs/therapeutants so that they can be evaluated and the data used to support FDA approval of the drug. However, it has become apparent that more rigorous and complete data collection and analysis are required to obtain new animal drug approvals or applications (NADAs) for aquatic species. The goal of the AADAP is to ensure continued progress towards obtaining FDA-approved and EPA-compliant new animal drugs for use in public and private aquaculture programs.

Table 1. Investigational New Animal Drug (INAD) exemptions available as of Fall 2011. Additional information on target species, dosage, withdrawal, drug source, etc. for each INAD is available at the AADAP website (*http://www.fws.gov/fisheries/aadap/home.htm*).

Name of drug	INAD use/purpose of data collection	Source of drug
Terramycin® 200 for Fish (oxytetracycline medicated feed)	Control mortality caused by bacterial diseases of fish and abalone; mark skeletal tissue of finfish.	Phibro Animal Health
Terramycin® 200 for Fish (oxytetracycline medicated feed for shrimp)	Control bacterial diseases of penaeid shrimp.	Phibro Animal Health
Aquaflor® (florfenicol)	Control mortality caused by bacterial diseases.	Merck Animal Health
Halmid® or Actamide® (chloramine-T)	Control mortality caused by bacterial diseases.	Western Chemical, Inc. B.L. Mitchell, Inc.
Reward® (diquat)	Control mortality caused by bacterial diseases.	Syngenta Crop Protection, LLC
Oxytetracycline Hydrochloride (oxytetracycline immersion)	Control mortality caused by bacterial diseases.	regional retail outlets
SE-Mark® (calcein)	Effectiveness of calcein to mark certain fish tissues via immersion baths.	Western Chemical, Inc.
LHRHa	Spawning aide.	Western Chemical, Inc.
Common carp pituitary	Spawning aide.	Stoller Fisheries Argent Laboratories
Catfish pituitary	Spawning aide.	Hybrid Catfish Company
Ovaplant (sGnRHa)	Spawning aide.	Western Chemical, Inc.
Slice® (emamectin benzoate)	Control mortality caused by external parasites.	Merck Animal Health
35% PEROX-AID® (H_2O_2)	Control mortality caused by ectoparasites.	Western Chemical, Inc.
17α-methyltestosterone	Effectiveness as a larval feed additive to produce more than 90% male tilapia.	Rangen, Inc.
AQUI-S® 20E (eugenol)	Effectiveness and safety as an anesthetic/sedative.	Western Chemical, Inc.
Benzoak® (benzocaine)	Effectiveness and safety as an anesthetic/sedative.	Frontier Scientific, Inc.

In addition, the AADAP conducts a drug research program that is focused on the generation of efficacy and target animal safety data required for NADAs. The AADAP leads a coordinated national effort to generate data, analyze results, compile final study reports, disseminate information and data, and manage all other aspects of requisite data submissions to the FDA in support of new animal drug approvals for aquatic species.

Conclusion

INAD exemptions contribute important drug efficacy and safety data that are used to support the future approval of new drugs for use in aquatic species. NIP participants recognize the responsibilities of all parties to properly use, account for, and safeguard investigational new animal drugs and to comply with study protocol requirements in the collection and submission of data. For more information on the National INAD Program, visit the AADAP website (*http://www.fws.gov/fisheries/aadap/home.htm*) or contact the National INAD Program Administrator:

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USDA United States Department of Agriculture National Institute of Food and Agriculture

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