STUDY PROTOCOL FOR AN AQUACULTURE INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR OXYTETRACYCLINE (PENNOX 343®) FOR IMMERSION THERAPY (INAD #9033)

Sponsor:

U.S. Fish and Wildlife Service, Fish and Aquatic Conservation

_____ _____

Sponsor Signature Date Approved

Manufacturer:

Pharmgate Animal Health
1800 Sir Tyler Dr
Wilmington, NC 28405

Office for Coordination of Pennox 343® INAD:

Aquatic Animal Drug Approval Partnership Program
4050 Bridger Canyon Road
Bozeman, MT 59715

Proposed Starting Date	July 1, 2007
Proposed Ending Date	December 31, 2026
Study Director	Ms. Bonnie Johnson

Clinical Field Trial Location:

Facility: _____

Investigator: _____

Table of Contents

STUDY PROTOCOL FOR AN AQUACULTURE INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR PENNOX 343® IMMERSION THERAPY UNDER INAD #9033

I. STUDY ID AND TITLE:

Clinical field trials to determine the efficacy of Pennox 343® immersion therapy to control mortality caused by certain bacterial diseases in cultured fish.

II. SPONSOR:

Dr. Marilyn Blair, U.S. Fish and Wildlife Service, Branch Chief, Aquatic Animal Drug Approval Partnership Program, 4050 Bridger Canyon Road, Bozeman, MT 59715; Phone: 406-994-9904; Fax: 406-582-0242; Email: marilyn_j_blair@fws.gov

Manufacturer:

Pharmgate Animal Health
1800 Sir Tyler Dr
Wilmington, NC 28405

Contact Person at Pharmgate Animal Health:

Dr. James Skinner
1800 Sir Tyler Dr
Wilmington, NC 28405
Phone: 402-330-6000
Email: james.skinner@pharmgate.com

Study Director: Ms. Bonnie Johnson, U.S. Fish and Wildlife Service, Aquatic Animal Drug Approval Partnership (AADAP) Program, 4050 Bridger Canyon Road, Bozeman, MT 59715; Phone: 406-994-9905; Email: bonnie_johnson@fws.gov

Principal Clinical Field Trial Coordinator: Ms. Paige Maskill, USFWS – AADAP Program
4050 Bridger Canyon Road, Bozeman, MT 59715;
Phone: 406-994-9911; Email: paige_maskill@fws.gov

Study Monitors: See Appendix II for names and addresses.

I. INVESTIGATORS/FACILITIES:

See Appendix IIIa for names and addresses.

IV. PROPOSED STARTING AND COMPLETION DATES:

Reauthorization Starting Date: July 1, 2007

Reauthorization Expiration Date: December 31, 2026

V. BACKGROUND/PURPOSE:

Oxytetracycline has historically been the drug of choice when diagnostic evidence shows salmonids to have furunculosis, caused by *Aeromonas salmonicida*; bacterial hemorrhagic septicemia, caused by *Aeromonas (liquefaciens) hydrophila* and other closely related bacteria; pseudomonas disease, caused by *Pseudomonas sp.*; enteric redmouth, caused by *Yersinia ruckeri*; flavobacteriosis, caused by *Flavobacterium columnaris (Flavobacterium columnaris), Flavobacterium psychrophilus*, or closely related yellow pigmented gliding bacteria as described in U. S. Food and Drug Administration (FDA) Public Master File #5456; or, vibriosis caused by *Vibrio anguillarum, Vibrio ordalli* or other closely related bacteria.

In warmwater fish culture, oxytetracycline also has been useful in the control of enteric septicemia of catfish, caused by *Edwardsiella ictaluri* and bacterial hemorrhagic septicemia, pseudomonas disease, and flavobacteriosis in catfish, sturgeon, temperate basses, sunfishes, and other fish species including several listed as threatened or endangered under the Endangered Species Act.

Integrated fish health management practices usually prevent the occurrence of these diseases. However, adverse environmental conditions, uncontrollable water supplies and unforeseen factors can lead to severe disease outbreaks requiring prompt treatment in order to prevent significant losses of fish valuable to natural resource stewardship. Such treatment also reduces the discharge of infectious agents into the natural environment thereby reducing the spread of disease. Treatment strategies for the use of oxytetracycline hydrochloride (Pennox 343®) in fish shall be designed to meet the needs of each species or lot, the size and numbers of fish to be treated, the layout of the facility, and environmental conditions. In all cases the objective shall be to minimize the impacts of disease on fish health, fish quality and survival, and to fully meet fishery management needs.

The purpose of this INAD is to develop clinical field trial data that will demonstrate the efficacy and safety of Pennox 343® to control mortality caused by certain bacterial diseases in cultured fish under a variety of environmental conditions, at a wide range of temperatures, and in a variety of fish species. These data will be used to support a new animal drug application (NADA) for Pennox 343®. Because there are many factors that can affect the success or failure of Pennox 343® immersion therapy, data is needed that will determine the best ways to use the drug. Drug dosages, treatment schedules, fish handling methods and other variables should be tested. Complete documentation of studies that are well conceived and well carried out will be of great value.

The U.S. Fish and Wildlife Service (USFWS) anticipates that it may require several years to carry out all clinical field trials and laboratory studies required to extend and expand the current label for Pennox 343® to cover major aquaculture needs. Therefore, the USFWS may request

that the U. S. Food and Drug Administration (FDA) grant re-authorization of this Pennox 343® INAD sometime in the future. In the interim, the USFWS will continue to work closely with the sponsor, the National Coordinator for Aquaculture New Animal Drug Applications, and other research and conservation agencies to develop other required New Animal Drug Application (NADA) research data to support expanded labels claims for Pennox 343®. Therefore, clinical field trials planned under this particular INAD are but one part of a larger coordinated and diligent inter-agency effort that will eventually meet all Pennox 343® NADA data requirements

VI. SPECIFIC OBJECTIVES:

The two major objectives of this study protocol are as follows:

1. Collect scientific data necessary to support pivotal efficacy trials to further establish the effectiveness of Pennox 343® immersion therapy to control mortality caused by certain bacterial diseases in cultured fish under a variety of environmental conditions, at a wide range of temperatures, and in a variety of fish species.

2. Provide an opportunity for fish culturists to legally use Pennox 343® immersion therapy to control certain bacterial diseases in cultured fish that occur under a variety of environmental conditions, at a wide range of temperatures, and in a variety of fish species so that they can maintain healthy stocks of fish during the period of time necessary for collection of data that will be used to support expanded label claims for the use of Pennox 343®.

VII. MATERIALS:

A. Test and Control Articles:

1. Drug Identity

a. Active ingredient

Common Name: Oxytetracycline hydrochloride

Product Name: Pennox 343® Soluble Powder

Chemical Family: Tetracycline derivative

CAS Number: 2058-46-0

Appearance: Yellow powder

Odor: None

b. Strength and dosage form

Pennox 343® is a broad-spectrum, highly concentrated antibiotic powder intended for administration in the drinking water of swine for the control of

specific diseases. It is also approved for use as an immersion treatment to mark the skeletal tissue of finfish fry and fingerlings (NADA 008-622). **Pennox 343® contains 343g of active oxytetracycline hydrochloride per pound of product.**

c. Manufacturer, source of supply

Pharmgate Animal Health (often available from your local farm and ranch store, veterinary supply outlet, etc.)
1800 Sir Tyler Dr
Wilmington, NC 28405

Contact person:

Dr. James Skinner
1800 Sir Tyler Dr
Wilmington, NC 28405
Phone: 402-330-6000
Email: james.skinner@pharmgate.com

Note: A veterinarian prescription is not needed when Pennox 343® is used under the INAD. Investigators will need to fill out Form OTIMM-W (study request) in the online database and advance the study to stage 3. AADAP will then review the study; assign a study number; then email a copy of the approved Form OTIMM-W to the supply company to show use will be under an INAD. The supply company will retain a copy of Form OTIMM-W for their records.

2. Verification of Drug Integrity/Strength:

The manufacturer, Pharmgate Animal Health, will provide the analytical data necessary to establish the purity of each lot of Pennox 343® supplied. The lot number and date of manufacture for each batch of Pennox 343® will be placed on the label of each container. The form "Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals" (Form OTIMM-1) will clearly identify the lot number and date of manufacture of Pennox 343® shipments. If the integrity of the Pennox 343® is compromised (i.e., by spilling or contamination of the stock container) the event will be carefully recorded, dated, and signed in the Chemical Use Log (Form OTIMM-2). All unusable Pennox 343® will be disposed of by following the Safety Data Sheet (SDS). The Study Monitor assigned to the Investigator involved will be immediately notified.

3. Storage Conditions

Pennox 343® must be stored in the original container supplied by the Manufacturer with the appropriate investigational label attached. The container should be stored out of direct sunlight in a well ventilated area at room temperature. The storage unit for Pennox 343® must be labeled to indicate that it contains hazardous material and that "*NO Food or Drink is to be Stored in this unit*".

4. Handling Procedures

Each Study Monitor and Investigator will be required to have a current copy of the Safety Data Sheet (SDS) for Pennox 343® (see Appendix IV). Each person involved with the study and each person who may be present during the use of Pennox 343® shall be required to read the SDS. Safety precautions as outlined in the SDS will be followed at all times when working with Pennox 343®.

5. Investigational Labeling

A copy of the label to be attached to each container of Pennox 343® medicated feed is provided in Appendix V. It is the responsibility of the Investigator to ensure proper labeling of all containers of Pennox 343®.

6. Accountability

Pharmgate Animal Health will be the sole supplier of Pennox 343® to all Investigators under INAD 9033. However, oxytetracycline hydrochloride often available from your local farm and ranch store, veterinary supply outlet, etc.

The Online INAD Database must be used by Investigators for ALL INAD reporting. The online INAD database has a built-in system of checks, balances, and email notifications to ensure that all information/data reporting and accountability follows established INAD Study Protocol guidelines. Unless data is entered directly into the online INAD database (i.e., not captured elsewhere at the time of observation or measurement and transcribed into the online INAD database) investigators must archive hard copies of all raw data.

1. All facilities using Pennox 343®:

   Immediately upon receiving an order/shipment of Pennox 343®, the Investigator must complete Form OTIMM -1 “Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals” (located in the “Manage/View Drug Inventory” section of the investigator account). The Study Director will forward a copy of this form to the FDA. Arrangements should be made between Investigators and Study Monitors to insure completed Form OTIMM-1s are received by the Study Director within 10 days of drug receipt.

   All Investigators are also responsible for maintaining an accurate inventory of Pennox 343® on-hand. A Chemical Use Log (Form OTIMM-2) must be completed and maintained by each Investigator. Each time Pennox 343® is used, it must be recorded by the Investigator in the Results Report form in the “Amount Of Drug Used” table.

   At the conclusion of field trials, all remaining Pennox 343® will be destroyed by following the SDS (note: unless diquat is planned for use in another approved field trial, and planned usage is within the storage guidelines established by the manufacturer). Disposition of all Pennox 343® must be properly recorded and

accounted for on the Chemical Use Log (Form OTIMM-2). The Study Monitor will be responsible for verifying the quantity of Pennox 343® remaining on hand versus the amount indicated on Form OTIMM-2. **Note:** Pennox 343® can be transferred to other facilities that are participating under INAD 9033 or transferred to approved agriculture labeled use. Transfers must be shown on Form OTIMM-2

7. Preparation Procedures

Oxytetracycline will be supplied to Investigators as Pennox 343® containing 343g of active oxytetracycline hydrochloride per pound of product. Hence, when calculating desired treatment concentration, Investigators should consider Pennox 343® to be 75.6% active oxytetracycline. Pennox 343® should not be adulterated in any manner prior to use.

B. Items Needed for Treatment, Data Collection, Etc.:

Sampling techniques and diagnostic equipment will most likely be provided by trained fish health biologists serving as Study Monitors or their designee(s). Equipment and supplies needed would include items to sample, culture, grow and identify culture growths microscopically. Standard fish culture supplies and equipment would also be required.

When the Study Protocol has been approved and treatments are scheduled, the Investigator at each facility covered by the Pennox 343® INAD will need to complete several forms located in the online INAD database. These forms are described in Section XIII. Copies of these forms are attached to this Study Protocol and will be used as a guide only for collecting the data that will be entered into the online INAD database.

VIII. EXPERIMENTAL UNIT

The experimental unit in this clinical field trial will consist of a contained or isolated group of fish. This will generally be a group of fish contained in a tank, raceway, or pond. In some cases, the experimental unit may be individual animals.

IX. ENTRANCE CRITERIA

A. Facilities/Investigators

The proposed facility and the Investigator must be listed in Appendix IIIa of the Study Protocol for the current calendar year before Pennox 343® can be ordered and dispensed under this INAD. Last minute deviations can be requested by the Sponsor, Study Director, or by an Investigator in case emergency use-pattern needs should arise (See Section XX). However, poor planning and/or a lack of preparation will not be considered an emergency situation.

B. The characteristics of the study animals (species, number, etc.) is presented in Appendix VIb.

C. Environmental conditions

Environmental conditions will be variable and include a broad spectrum of water temperatures and water quality parameters. Environmental conditions will be reported on a Form OTIMM-3. Drug discharge must be in compliance with local **NPDES** permitting requirements.

D. Ability of Investigator to fulfill all the requirements of the Study Protocol

See Appendix IIIb for example of knowledge required of hatchery managers (i.e., Investigators).

Prior to initiating each treatment event, the Investigator must first complete Form OTIMM-W. “Worksheet for Designing Individual Field Trials” (located under the “New Study Request” tab in the investigator account) that pertains to each specific treatment event. The worksheet should be filled out and forwarded to the Study Monitor through the online INAD database. The Study Monitor will review the planned treatment (worksheet) and forward it to the Study Director at the AADAP Office. The Study Director will then review the worksheet, assign the approved treatment a Study Number, and then the online INAD database will notify both the Investigator and the Study Monitor of the assigned number and approval to proceed. In most cases, this entire process should be able to be accomplished within a single working day. After initiation of the field trial, the Investigator should also record the assigned study number on any paper forms that are being used as a guide to collect the data to enter in the online database (i.e., Form OTIMM-2 and OTIMM-3), as well as on any additional correspondence regarding that specific treatment event. If for some reason the Investigator is unable to reach the Study Monitor with regards to Worksheet approval and the need for treatment is immediate, the Investigator should contact the AADAP Office for permission to proceed.

Note: The online INAD database, which must be used by Investigators for all INAD reporting, has a built-in system of checks, balances, and email notifications to ensure that all information/data reporting follows established INAD Study Protocol guidelines.

E. Pathogen/disease considerations

a. Bacterial fish pathogens should be presumptively identified by procedures described in Section 3 of the "Blue Book" (Procedures for the Detection and Identification of Certain Fish Pathogens, Third Edition, Fish Health Section/American Fisheries Society, 1985). Other, more sensitive methods described elsewhere in peer-reviewed references, or as mutually determined by the local fish health biologist, in consultation with the Study Monitor, also may be used. (**Note**: **Diagnostic methods other than those in the Third Edition of the "Blue Book" should be described on a separate sheet attached to a Form OTIMM-3 “Results Report Form”**).

b. There should be increased mortality rates among fish in a rearing unit(s) for three or more consecutive days. (Note: Station history and the experience of the investigator, monitor, or the fish health biologist may over-ride this criterion to halt potentially explosive disease outbreaks. In such cases, however, careful diagnostic surveillance should be carried out in all rearing units proposed for treatment and controlled tests should be carried out if at all possible.)

c. Typical disease signs should be detectable in at least a few fish and the causative pathogen should be identified.

X. TREATMENT GROUPS

A. A treatment group or experimental unit may be an entire tank, pond, raceway, or group of fish, or it may be individual animals.

B. Non-treated control groups will not be a requirement for clinical field trials evaluating the efficacy of Pennox 343® due to the following conditions:

1. Outbreaks of BGD or flavobacteriosis often occur in only one tank or raceway at a time.

2. BGD is often so virulent that epizootic-type mortality can be expected in untreated controls. Flavobacteriosis that occurs under stressful culture conditions can also result in epizootics if the disease organism is not controlled.

3. Separating diseased fish into control and treatment groups may not only increase the stress placed on fish, but may also change environmental conditions such as population density, water quality, etc. These factors may impact the rate of progression of BGD and flavobacteriosis. Although it may be possible to minimize such bias by transferring two sub-groups of "sick" fish into two separate, but equal tanks (where one group will receive treatment and the second will serve as a non-treated control), such "study design" is not an option at many facilities. Furthermore, as diseased fish are reservoirs of flavobacterial infection, whenever fish are transferred to new rearing units, the potential for infection is increased.

C. Although as stated above untreated control groups are not a required element of treatment under this INAD exemption, **it is important for all investigators to note that field trials conducted under a more stringent study protocol (i.e including requirements for non-treated controls groups, replication, blinding, dose verification, etc.) will ultimately be required in order to support a NADA for Pennox 343®. It is also important to note that the INAD sponsor fully expects that a limited number of facilities/investigators listed under this INAD exemption will agree to participate in such "pivotal" efficacy studies.** These studies will be initiated only after direct consultation between facilities/investigators and the sponsor. These studies will be conducted under a separate FDA-approved study protocol (i.e. not the INAD study protocol), and will also be conducted with

assistance from, and under the direct supervision of, the sponsor. **If for any reason it becomes apparent to the sponsor that facilities/investigators listed under this INAD are not willing to participate in such "pivotal" studies, the sponsor will request that FDA terminate the INAD.**

XI. TREATMENT SCHEDULES

A. Route of administration

Pennox343® will be administered only as an immersion treatment.

B. Dosage, treatment duration, and dosing interval/repetition

Objective A [For the control of furunculosis, bacterial hemorrhagic septicemia, enteric redmouth, flavobacteriosis, and vibriosis in a variety of salmonid fish species]

Treatment at 20 mg oxytetracycline per liter of water for 1 hour.

A single treatment event with no repetition.

Objective B [For the control of enteric septicemia in catfish, and bacterial hemorrhagic septicemia, pseudomonas disease, and flavobacteriosis in catfish, sturgeon, temperate bass, and other cool and warmwater fish species]

Treatment at 20 mg oxytetracycline per liter of water for 1 hour.

A single treatment event with no repetition.

Objective C [For the control of furunculosis, bacterial hemorrhagic septicemia, enteric redmouth, flavobacteriosis, and vibriosis in a variety of salmonid fish species]

Treatment at 20 mg oxytetracycline per liter of water for 1 hour.

One to four treatments administered on consecutive days.

Objective D [For the control of enteric septicemia in catfish, and bacterial hemorrhagic septicemia, pseudomonas disease, and flavobacteriosis in catfish, sturgeon, temperate bass, and other cool and warmwater fish species]

Treatment at 20 mg oxytetracycline per liter of water for 1 hour.

One to four treatments administered on consecutive days.

C. Drug preparation and administration procedures

Oxytetracycline will be supplied to Investigators as Pennox 343® containing 343g of active oxytetracycline hydrochloride per pound of product. Hence, when calculating desired treatment concentration, Investigators should consider Pennox 343® to be 75.6% active oxytetracycline. Pennox 343® should be thoroughly mixed in rearing unit water. Pennox 343® should not be adulterated in any manner prior to use.

D. Permissible concomitant therapy

Since efficacy data are being collected during the INAD process, there should be little or no concomitant therapy. Preferably, there should be no other therapy during a period extending from 2 weeks prior to treatment to 2 weeks after treatment. Investigators must be prepared to minimize changes in fish cultural procedures or environmental conditions, and apply no other treatments following treatment with Pennox 343®.

However, if concomitant therapy is required in order to protect valuable fish stocks (i.e., threatened and endangered species not for human consumption) it should be fully documented and the efficacy data from the Pennox 343® treatment involved should be appropriately labeled. Contact the AADAP Office for the information that will need to be provided in the Form OTIMM-3 if concomitant therapy is conducted.

XII. TREATMENT RESPONSE PARAMETERS

The collection and reporting of source data begins with the decision to treat valuable fish based on hatchery records or field management practices that indicate treatment is warranted. Daily morbidity and mortality records, case history records, as well as any extenuating or mitigating circumstances that may affect treatment response need to be documented. All pertinent treatment response parameters should be reported on Form OTIMM-3. Treatment response parameters that should be addressed include the following:

1. Primary Parameters

Morbidity and mortality data, coupled with case history and analyses of bacterial load, usually indicate when Pennox 343® treatment is needed. **Source data must be collected for 5 days before treatment, during treatment, and for 10 days after the treatment period has ended**. Collection of this data is critically important. Samples of kidney or other tissue should be removed from groups of representative fish and tested by bacteriological, serological, or other methods to determine the presence of target pathogens.

2. Secondary Parameters

Secondary parameters may also include general observations on fish behavior and response to routine culture/handling activities. This would include such responses as feeding activity, feed consumption, apparent level of stress, negative fish behavior, etc.

3. Adverse Reactions

Any adverse reaction to treatment should be reported **immediately** to the Study Monitor, who will in turn notify the Study Director. Such responses might include extremely negative responses/behavior by the fish or hazards to the applicator. Although Pennox 343® immersion therapy has been used extensively for many years with beneficial effect in fish culture, it is possible adverse reactions may occur under certain environmental conditions or with respect to specific species/strains of fish. Carefully observe all treated fish for any signs of any adverse reaction to treatment. The Investigator should carefully document all observations of adverse reactions. **If any signs of drug toxicity are detected, they should also be documented and immediately reported to the Study Monitor, who will in turn notify the Study Director.**

Note: Investigators are strongly encouraged to record observations/comments with respect to all phases of treatment. This may include a description of events before, during, and post-treatment. All extenuating or mitigating treatment circumstances need to be described in detail. Such information is imperative so that accurate study/data analysis can be performed.

XIII. FORMS FOR DATA COLLECTION

When the Study Protocol has been approved and treatments are scheduled, the Investigator at each facility covered by Pennox 343® INAD 9033 will need to complete the following forms:

Form OTIMM-W. Worksheet for Designing Individual Field Trials under Pennox 343® INAD 9033 - located in the New Study Request tab

Form OTIMM -1. Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals – located in the Manage/View Drug Inventory tab

Form OTIMM -2. Chemical Use Log for Clinical Field Trials under Pennox 343® INAD 9033 – located in the Manage/View Drug Inventory tab and filled out in Form OTIMM-3 to show use

Form OTIMM -3. Results Report Form for Use of Pennox 343® INAD 9033 – located in the Active Studies table on the home page

Copies of these forms are attached to this Study Protocol. Actual reporting is accomplished on forms located in the online INAD database.

XIV. RECORD KEEPING PROCEDURES

As stated immediately above, all data reporting are accomplished via forms located in the online INAD database. All current and completed studies conducted under the investigator account will be stored and available in the online INAD database to the current study monitor, study investigator, and AADAP.

XV. DISPOSITION OF INVESTIGATIONAL ANIMALS

Animals that die during treatment should be disposed of by burial or incineration. All fish treated with Pennox 343® must be maintained in culture facilities for a specified withdrawal time following completion of therapy before stocking/release or harvest. Specific withdrawal time is based upon treatment objective as defined in Section XI.B of this study protocol and are as follows:

Objective A: 21 days

Objective B: 21 days

Objective C: 60 days

Objective D: 60 days

No withdrawal period will be required for fish that will not be catchable for the 21 days or more for objectives A or B or 60 days or more for objectives C or D after release, or are illegal for harvest.

The Investigator must verify compliance with requirements regarding the disposition of all treated fish on Form OTIMM-3.

XVI. DISPOSITION OF INVESTIGATIONAL DRUG

Pennox 343® will be used only in the manner and by the individuals specified in the Study Protocol. If any unused Pennox 343® remains at the end of the study period, Investigators should contact Study Monitors for instructions regarding drug disposal. Drug disposal information is available in the Safety Data Sheet (SDS) located in Appendix IV of this protocol. Disposition of all Pennox 343® must be properly recorded and accounted for on the Chemical Use Log (Form OTIMM-2). The Study Monitor will be responsible for verifying the quantity of Pennox 343® remaining on hand versus the amount indicated on Form OTIMM-2. The investigational drug may not be redistributed to others not specified by the protocol and should not be retained by the Investigator after completion of the study (note: unless Pennox 343® is planned for use in another approved field trial, and planned usage is within the storage guidelines established by the manufacturer). The investigational drug may not be redistributed to others not specified in the Study Protocol. Transfers must be shown on Form OTIMM-2.

XVII. DATA HANDLING, QUALITY CONTROL, MONITORING, ADMINISTRATIVE RESPONSIBILITIES

A. Drug distribution

See Section VII.A.6. Accountability for information and details.

B. Study Monitors

Study Monitors are generally fish health professionals with experience in diagnosing and treating fish diseases, and the ability to monitor overall fish health with respect to ongoing fish culture practices. A study monitor will be selected by each facility that is authorized to treat fish with Pennox 343® under this INAD. A list of Study Monitors, along with addresses and phone numbers, can be found in Appendix II. Study Monitors are responsible for supervision of the trials, adherence of the Investigator to the Study Protocol, and inspection of the site.

C. Special equipment and materials

Most of the equipment and materials required for this study (with the exception of the Pennox 343® itself are already available at each participating fish hatchery. The use of various drugs, chemicals, and therapeutants to meet management and/or production goals is a common occurrence at most fish hatcheries. Fish hatchery managers (i.e., Investigators) are well trained and well equipped to handle these situations (see Appendix IIIb). If any additional equipment or materials are required, they will be provided by the Study Monitors (See Section VII.B. Items needed for sample collection, observations, etc.).

D. Administrator of the drug

Pennox 343® will be administered directly by the assigned Investigator (fish hatchery manager) or under the Investigator's direct supervision (see Appendix IIIa for names). Pennox 343® will be maintained in a secure location, and only the Investigator or persons under his/her direct supervision will have access.

E. Drug accountability records

See Section VII.A.6. Accountability for details and the following forms will be used as guides for data collection: Form OTIMM-W, Form OTIMM-1, Form OTIMM-2, and Form OTIMM-3.

F. Recording observations

The Investigator or a person under his/her direct supervision will be responsible for implementing the Study Protocol, making observations, collecting samples, and recording data during the clinical field trials. After the data have been collected and recorded on the forms, the Investigator will send the data to the Study Monitor who will ensure that all required information is provided. The Study Monitors will in turn send the data to the Study Director. The Study Director will analyze and summarize the data and prepare summary reports that will be submitted to the FDA. **Note: If the Study Monitor does not think all required information has been provided, or forms have not been satisfactorily completed, he/she should contact the Investigator and rectify the situation before forwarding the package to the Study Director.**

G. Data storage

The Investigator is responsible for complete and accurate data collection, and must complete all required data forms (see protocol Section XIII). The Investigator should forward all completed forms to the Study Monitor for review. Study Monitors should

carefully check each set of data for accuracy and completeness. If a form is incomplete or inaccurate, it should be returned to the Investigator. If a form is complete and accurate, it should be forwarded to the Study Director at the AADAP Office. **Note:** data that is entered through the online INAD database will be archived in the database. These archived forms will be available as long as the study participant accounts remain open.

XVIII. PLANS FOR DATA ANALYSIS

Data analysis will be completed by the Study Director located at the AADAP Office. Data from the treatment year will be summarized through tabulation and appropriate statistical analysis. INAD reports will be prepared and submitted to the FDA as required. This submission may include a request for an extension of the INAD based on the data collected during that year. When sufficient data are collected, the entire INAD data set will be summarized in a final report for submission to support a full NADA.

XIX. PROTOCOL AND PROTOCOL AMENDMENTS

A signed copy of the Study Protocol must be retained by each Investigator. At any time before a field trial begins, desired changes in the Study Protocol should be brought to the attention of the Study Director. The desired changes will be fully described in the form of an amendment along with the reason for the change. The amendment will be signed by the Sponsor (or its representative) and forwarder to the FDA for review. Copies of the signed amendment will be attached to each copy of the Study Protocol. **Investigators will be liable for non-compliance violation if drugs are used without a Study Protocol or in a manner different than specified in the Study Protocol, if forms are not filed on time, or if the study data are not properly collected, maintained, and reported.** The Study Monitor is responsible for ensuring that all INAD procedures are being followed as defined by the Study Protocol.

XX. PROTOCOL DEVIATIONS

Deviations from the established Study Protocol occasionally cannot be avoided. If deviations occur, the Study Monitor should be notified immediately. **Protocol deviations should be fully documented and should be accompanied by a written explanation of what happened, why, and what steps were taken to mitigate the deviation.** Deviations should be documented on Form OTIMM-3 in the *Description of Results* section and in the *Study Deviation* field.

XXI: E.O. 13891

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way. This document is intended only to provide clarity to the public regarding existing requirements under the law or agency policies.

Appendix I. Sponsor Contact Information for Pennox 343® INAD #9033

Sponsor: Dr. Marilyn Blair, U.S. Fish and Wildlife Service, Aquatic Animal Drug Approval Partnership (AADAP) Program
Phone: (406) 994-9904
Fax: (406) 582-0242
Email: marilyn_j_blair@fws.gov

Sponsor Address: 4050 Bridger Canyon Road, Bozeman, MT 59715

Study Director: Ms. Bonnie Johnson
Aquatic Animal Drug Approval Partnership (AADAP) Program
Phone: (406) 994-9905
Fax: (406) 582-0242
Email: bonnie_johnson@fws.gov

Principal Clinical Field Trial Coordinator: Ms. Paige Maskill
Aquatic Animal Drug Approval Partnership (AADAP) Program
Phone: (406) 994-9911
Fax: (406) 582-0242
Email: paige_maskill@fws.gov

1

Appendix II. Study Monitors for Pennox 343® INAD #9033

Note: This information will be provided directly to CVM

1

1Appendix IIIa. Facilities and Names of Investigators Participating under Pennox 343® INAD #9033

Note: This information will be provided directly to CVM

Appendix IIIb. Sample of Knowledge Required for Position of Hatchery Manager (i.e. Investigators)

Professional knowledge of all facets of fishery biology as well as the ability to apply new scientific findings, developments, and advances toward the resolution of critical propagation problems involving the rearing a variety of fish species under a variety of water quality conditions, water temperatures, water chemistry, etc.

Knowledge of general bacteriology, parasitology, and water chemistry sufficient to treat fish for various diseases.

Skill in interpreting biological observations and ability to draw sound conclusions from available data.

Skill in developing and coordinating available resources to ensure effective management and utilization of manpower, equipment, and funds relative to established priorities and needs.

Skill in coordination of sometimes divergent resource issues to obtain common objectives, including interaction with other Federal, State, Tribal, and private agencies/facilities.

Knowledge of and skill in the use of effective management and supervisory techniques to provide support, guidance, and motivation to hatchery staff.

1

Appendix IV. Material Safety Data Sheet (MSDS) for Pennox 343® INAD #9033

The SDS for Pennox 343® can be found at the drug sponsor's website

Pennox 343_(USA)_EN_sds (pharmgate.com)

1

Appendix V. Investigational Label for Pennox 343® INAD #9033

1. Investigational label for tests in vitro and in laboratory research animals [511.1(a)]:

   "Caution. Contains a new animal drug for investigational use only in laboratory animals or for tests in vitro. Not for use in humans."

2. Investigational label for use in clinical field trials [511.1(b)]:

   "Caution. Contains a new animal drug for use only in investigational animals in clinical field trials. Not for use in humans. Edible products of investigational animals are not to be used for food unless authorization has been granted by the U.S. Food and Drug Administration or by the U.S. Department of Agriculture."

1

Appendix VIa. Fish Species Treated under Pennox 343® INAD #9033

Freshwater finfish
Marine finfish

1

Appendix VIb. Table of Facilities and Fish Stocks Treated under Pennox 343® INAD #9033

Note: This information will be provided directly to CVM

All data must be entered through the online INAD database:

The following forms are to be used as a guide for collecting data that will be entered into the **online INAD** d**atabase**. Any paper forms that are submitted to AADAP will be sent back to the study participants.

Form OTIMM-W: Worksheet for Designing Individual Field Trials under Pennox 3437 INAD 9033

INSTRUCTIONS

1. Investigator must fill out Form OTIMM-W for each trial conducted under this INAD **before** actual use of Pennox 343®.
2. Investigator should forward a copy of OTIMM-W to the Study Monitor for review.
3. After review, the Study Monitor should forward a copy to the AADAP Office for review and assignment of the Study Number.

SITE INFORMATION

Facility			
Address			
Investigator			
Reporting Individual (if not Investigator)			
Phone		Fax	

FISH CULTURE AND DRUG TREATMENT INFORMATION

Fish species to be treated		Disease to be treated	
Average fish weight (gm)		Average fish length (in)	
No. of fish per unit (e.g. 10,000 fish/raceway)			
Number of treated units		Number of treated fish	
Number of untreated control units		Number of control fish	
Anticipated date treatment will be initiated		Anticipated number of treatment	
Intended drug target dosage (mg/L)	**20**	Estimated total weight of fish treated (lbs)	
Estimated total amount of drug needed for proposed treatment (gm)		Planned duration of drug treatment (hours)	**1**
Drug manufacturer		Drug lot number	

STUDY DESIGN: Provide a brief description of your planned study. The description should include the reason you feel fish should be treated, the treatment dates, the number of fish that will be treated, and if the fish are a threatened or endangered species.

Study designed by _____

DISPOSITION OF TREATED FISH (Human Food Safety Considerations):

_____ Estimated time (days, months) from last treatment day to first possible harvest for human consumption

Check applicable box(es):

☐ Study Objective A - Withdrawal period of 21 days for variety of salmonid fish.

☐ Study Objective B - Withdrawal period of 21 days for non-salmonid fish.

☐ Study Objective C - Withdrawal period of 60 days for variety of salmonid fish.

☐ Study Objective D - Withdrawal period of 60 days for non-salmonid fish.

☐ Investigator should initial here to indicate awareness that fish disposition must be in compliance with FDA-mandated withdrawal times as described in Section VI of the Study Protocol.

WORKER SAFETY CONSIDERATIONS:

☐ Investigator should initial here to indicate that all personnel handling drug have read Safety Data Sheet for Pennox 343® and have been provided protective equipment, in good working condition, as described in the SDS.

Date Prepared: _____ **Investigator:** _____

Date Reviewed: _____ **Study Monitor:** _____

FORM OTIMM-1. Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals

INSTRUCTIONS

1. Investigator must fill out Form OTIMM-1 **immediately** upon receipt of Reward®.
2. Investigator should forward a copy of Form OTIMM-1 to the Study Director at the AADAP Office.

The sponsor, U.S. Fish and Wildlife Service, submits a notice of claimed investigational exemption for the shipment or delivery of a new animal drug under the provisions of Section 512 of the Federal Food, Drug, and Cosmetics Act. The following information is submitted to the FDA:

Name of Drug	**Pennox-343**	INAD Number	**9033**
Proposed Use of Drug	Treatment of certain bacterial diseases that occur in a variety of fish species		
Date of CVM Authorization Letter	August 19, 2016		
Date of Drug Receipt		**Amount of Drug Received**	
Drug Lot Number		**Study Worksheet Number**	
Name of Investigator			
Address of Investigator			
Location of Trial			
Pivotal Study (yes/no)		Non-pivotal Study (yes/no)	
Approximate Number of Treated Animals		**Approximate Number of Control Animals**	
Number of Animals Used Previously[1]			
Study Protocol Number	9033		
Approximate dates of trial (start/end)			
Species, Size, and Type of Animals			
Maximum daily dose and duration	20 mg/L for 1hour		
Methods(s) of Administration	Immersion (static bath treatment 1 - 4 days)		
Withdrawal Period	21 days for 1 day treatment; 60 days for 2 - 4 day treatment		

[1] To be filled out by the NIO

Date Prepared: _____ **Investigator:** _____

Date Reviewed: _____ **Study Monitor:** _____

Date Reviewed: _____ **Sponsor:** _____

Form OTIMM-2: Chemical Use Log for Clinical Trials Using Pennox 343[7]under INAD 9033

INSTRUCTIONS

1. Investigator should initiate a new form OTIMM-2 **immediately** upon receipt of each shipment of Pennox 343®.
2. Each lot number of Pennox 343® may be used for multiple treatment regimens.

Qty of Pennox 343® from previous page (gml) _____ Facility _____ Reporting Individual _____

Date	Amount of new TM-343 received (gm)	Lot number of TM-343 received	Study Number	Amount of TM-343 used in treatment (gm)	TM-343 transferred (gm)	TM-343 discarded (gm)	TM-343 remaining on hand (gm)	Inventory by (Initials)
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						

Date Prepared: _____ **Investigator:** _____

Date Reviewed: _____ **Study Monitor:** _____

1**Form OTIMM-3: Results Report Form for use of Pennox 343® under INAD 9033**

1**INSTRUCTIONS**

1. Investigator must fill out Form OTIMM-3 no later than 30 days after completion of the study period. Attach lab reports and other pertinent information.
2. If Pennox 343® was not used under the assigned Study Number, contact the Study Director at the AADAP Office on how to close-out the study.
3. Investigator should forward a copy of Form OTIMM-3 to the Study Monitor. Within 10 days of receipt, the Study Monitor should forward a copy to the Study Director at the AADAP Office.

SITE INFORMATION

Facility	
Reporting Individual	

TREATMENT INFORMATION AND SCHEDULE

Drug lot number		Total amount drug used (gm)	
Fish species treated		OTIMM dosage used (mg/L)	**20**
Duration of drug treatment (hours)	**1**	Number of treatments	
Disease treated		Disease diagnosed by	
Average fish weight (gm)		Average fish length (in)	
Number of fish per unit (e.g. 10,000 fish/raceway)			
Number of treated units		Total number of treated fish	
Number of control units		Total number of control fish	
Treatment date(s)			

WATER QUALITY PARAMETERS

Ave pre-treatment temp (^{o}F)		Dissolved Oxygen (mg/L)	
Ave treatment temp (^{o}F)		pH	
Ave post-treatment temp (^{o}F)		Hardness - $CaCO_3$ (mg/L)	

Daily Mortality Record

INSTRUCTIONS

1. Investigator should fill out the Daily Mortality Record as completely as possible.
2. Prior to initiation of the trial, fill out Rearing Unit ID, whether a rearing unit is **T**reated or **C**ontrol, and the number of fish in each rearing unit.
3. Water temperature and individual tank mortality should be recorded on a daily basis.
4. If treatment is on 3 consecutive days, fill in only days 1-3 of the "treatment period" and proceed directly to day 1 of the "post-treatment period". If less than 3 treatments are used, proceed directly to day 1 of the "post-treatment period" after the final treatment. Please mark all treatment days with an asterisk.
5. **Even if mortality is zero an entry is still needed for that day.**

1**FACILITY**										
	Rearing Unit ID									
	Treated or Control									
	Number of Fish									
	Day	**Date**	**Water Temp (F°)**	**Mortality**	**Mortality**	**Mortality**	**Mortality**	**Mortality**	**Mortality**	**Daily Observer Initials**
Pre-treatment period	1									
	2									
	3									
	4									
	5									
Treatment period	1									
	2									
	3									
	4									
Post-treatment period	1									
	2									
	3									
	4									
	5									
	6									

1**FACILITY**									
	Rearing Unit ID								
	Treated or Control								
	Number of Fish								
Post-treatment period	7								
	8								
	9								
	10								

RESULTS: Describe in detail treatment results. Was treatment successful? If treatment did not appear to be successful, explain why not? Were there any mitigating environmental conditions that may have impacted treatment results? Were there any deviations from the Study Protocol?

Pathology Report: Attach pathology report to this form. Report should include: 1) a description of how the pathogen(s) was identified; 2) disease identification records that confirm the presence of the pathogen; and 3) the name and title of the individual performing the diagnosis.

Pathology Report included: ☐ pre-treatment ☐ post-treatment

Toxicity observations: Report any apparent drug toxicity including a description of unusual fish behavior.

OBSERVED WITHDRAWAL PERIOD: (Investigator should initial the appropriate box below)

Observed withdrawal period: _____ **21 days; Objectives A & B**

Observed withdrawal period: _____ **60 days; Objectives C & D**

Estimated number of days between last treatment and first availability of fish for human consumption (ensure this time period meets the withdrawal period). _____

☐ **NEGATIVE REPORT** Pennox 343® was not used at this facility under this Study Number during the reporting period. The study will be closed out in the online INAD database.

Date Prepared: _____ **Investigator:** _____

Date Reviewed: _____ **Study Monitor:** _____

NOTICES

Paperwork Reduction Act

In accordance with the Paperwork Reduction Act (44 U.S.C. 3501 *et seq.*), the U.S. Fish and Wildlife Service collects information necessary to permit the use of an investigational new animal drug to generate data to support a new animal drug approval (NADA) as part of the Fish and Aquatic Conservation fish health network. Your response is voluntary, but is required to obtain or retain a benefit. According to the Paperwork Reduction Act of 1995, an agency may not conduct or sponsor and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. OMB has approved this collection of information and assigned Control No. 1018-####.

ESTIMATED BURDEN STATEMENT

We estimate public reporting for this collection of information to average 4 hours, including time for reviewing instructions, gathering and maintaining data, and completing and reviewing the form. Direct comments regarding the burden estimate or any other aspect of the form to the Service Information Clearance Officer, Fish and Wildlife Service, U.S. Department of the Interior, 5275 Leesburg Pike, MS: PRB (JAO/3W), Falls Church, VA 22041-3803, or via email at Info_Coll@fws.gov. Please do not send your completed form to this address.

FREEDOM OF INFORMATION ACT STATEMENT

Information provided to the Service is generally subject to release to the public under the Freedom of Information Act (FOIA). Certain information, however, may be subject to withholding if the Service determines that the information is a trade secret and/or commercial or financial information that is privileged or confidential. To the extent you are submitting business information that falls into one of these categories, you must clearly mark this information as "Business Confidential" in order for the Service to assess the applicability of FOIA Exemption 4. Any information provided by you that is not marked as “Business Confidential” will be considered releasable to the public under the FOIA [43 CFR 2.26 – 2.33].