

**STUDY PROTOCOL FOR A COMPASSIONATE AQUACULTURE
INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION
FOR SLICE® (EMAMECTIN BENZOATE)
(INAD #11-370)**

Sponsor:

U.S. Fish and Wildlife Service, Division of Fish Hatcheries

Sponsor Signature

Date Approved

Manufacturer:

Merck Animal Health
35500 W. 91st Street
De Soto, KS 66018

Facility for Coordination of SLICE® (Emamectin Benzoate) INAD:

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

Proposed Starting Date

May 1, 2010

Proposed Ending Date

December 31, 2026

Study Director

Ms. Bonnie Johnson

Clinical Field Trial Location:

Facility: _____

Investigator: _____

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**STUDY PROTOCOL FOR A COMPASSIONATE AQUACULTURE
INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR SLICE®
(EMAMECTIN BENZOATE) UNDER INAD #11-370**

I. STUDY ID AND TITLE

Clinical field trials to determine the efficacy SLICE® of (emamectin benzoate) administered in feed to control mortality caused by external parasites in a variety of freshwater fish species. INAD 11-370.

II. SPONSOR

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INAD Study Monitors: See Appendix II for names and addresses.

III. INVESTIGATORS/FACILITIES

See Appendix IIIa for names and addresses. It is important to note that all facilities need to be approved by the FDA/CVM Environmental Team prior to participation in the INAD. If any of the approved conditions (i.e., number of treated fish; number of treatments each year; discharge of treated water; etc...) changes at your facility then a new approval will be required.

IV. PROPOSED STARTING AND COMPLETION DATES:

Proposed Starting Date: May 1, 2010

Proposed Completion Date: December 31, 2026

V. BACKGROUND/PURPOSE

External parasites form one of the largest groups of pathogenic organisms in cultured aquatic species. Affected species include finfish (freshwater and marine) and invertebrates. Environmental conditions such as temperature change and high organic loading in culture systems due to intensive fertilization and feeding levels increase the incidence and spread of many external parasites. Parasitic infections cause substantial economic losses to aquaculturists if not controlled. Many culturists have learned that some parasites can kill an entire population in a short time.

The organisms responsible for major parasitic infections on fish are, for the most part, protozoan and metazoan. These organisms are highly opportunistic and generally cause little pathology under normal conditions (e.g., in wildstock populations). However, under intensive culture where large numbers of fish are present, many of these organisms can cause serious disease problems.

Parasitic infections of fish, if not treated, can cause major losses and affect the restoration and preservation of depleted stocks of fish cultured by the U.S. Fish and Wildlife Service (USFWS). The extent of losses of fish from parasites depends upon the severity of the primary cause of infection. Morbidity can vary from less than 10% to total loss of the population (Post 1987). Historically, immersion treatments (static and flush) using a variety of compounds have been used to control mortality caused by parasite infestations. A number of the unapproved compounds (and/or concoctions) have been found to be relatively effective.

In 1986, the U.S. Food and Drug Administration (FDA) approved a new animal drug application (NADA) for the use of formalin to control external parasites (*Ichthyophthirius*, *Chilodonella*, *Costia*,

Scyphidia, *Epistylis*, *Trichodina*, *Cleidodiscus*, *Gyrodactylus*, and *Dactylogyrus*) on several fish species (salmonids, catfish, largemouth bass, and bluegill) and to control fungal infections on the eggs of salmon, trout and esocids. This decision by FDA was based on data that illustrated formalin was effective against those disease organisms and safe to use on those species allowed on the label. More recently, this label claim was expanded to include “.....for use on all finfish”.

While formalin has proven to be an effective parasiticide, it is not an aquatic species parasite control panacea, nor is it likely the drug-of-choice in all situations. As is the case with the treatment of virtually all pathogens (in both terrestrial and aquatic species), it is beneficial to have access to alternative treatment regimens to meet case-specific needs. A single drug for the control of mortality caused by external parasites will simply will not meet all needs of the aquaculture community. While an effective parasiticide, formalin use is somewhat limited by species specific effectiveness and toxicity issues. Furthermore, as formalin use as a parasiticide is an immersion treatment and formalin is not the most environmentally friendly compound, there have been increasing concerns over time (particularly at the individual State level) with regards to the discharge of formalin-treated water from aquaculture facilities. It is unlikely that this concern over the discharge of formalin in hatchery effluents will soon (if ever) reverse itself. SLICE® is an in-feed treatment that was developed specifically for the control of sea lice infestations in farmed salmon and trout. Control of sea lice (including *Lepeophtheirus salmonis*, *Caligus elongatus*, *C. rogercressyi*, and *C. teres*) on farmed fish is essential as lice feeding activity may result in mortalities, as well as susceptibility to a variety of other pathogens. SLICE® has been extensively tested in trials to evaluate environmental safety, efficacy, and tolerance in Atlantic salmon, *Salmo salar*, rainbow trout, *Oncorhynchus mykiss*, and brown trout, *Salmo trutta* in the marine environment (Stone et al., 1999; Stone et al., 2000a; Stone et al., 2000b; Stone et al., 2000c; Stone et al., 2002; Roy et. al., 2000; and Armstrong et. al., 2000). Currently, SLICE® is approved for the control of sea lice in salmonid species in the UK, Europe, Norway, and Chile.

The active component of SLICE® is emamectin benzoate. Emamectin is an avermectin developed initially for food crop use and is derived synthetically from avermectins which are produced by fermentation of the soil organism *Streptomyces avermitilis*. When emamectin benzoate is fed to fish it is absorbed from the gut and distributed to a variety of tissues. When sea lice (or other parasites) feed on the skin, mucus, blood, and muscle of the host fish, emamectin is taken up into the tissues of the louse. It then binds to ion channels of nerve cells and disrupts transmission of nerve impulses which results in paralysis and death of the parasite. Furthermore, emamectin benzoate is excreted slowly by the fish or metabolized to inactive compounds, resulting an extended period of protection from lice, long after medicated feed treatment has been completed (Stone et al., 2000c). This extended period of protection may extend up to 9 weeks post-treatment, thus making SLICE® a very attractive candidate for long-term parasite control.

Although SLICE® has been used most extensively for the control of sea lice in the marine environment, SLICE® has also been shown to be effective (and safe) when used to control sea lice on fish transferred from salt water and held in freshwater. It has also been shown to be effective (and safe) when used to treat naive smolts that are being maintained in freshwater

immediately prior to transfer to saltwater. The “extended period of protection” provided by SLICE® affords the highly susceptible smolt stage a better chance of surviving the many rigors associated with transfer to salt water (Stone et al., 2002).

In addition, more recently SLICE® has been used to effectively control mortality caused by freshwater parasites in salmonid species (Hakalahti et al., 2004 and Duston and Cusak, 2002). SLICE® has been found to be very effective for the treatment of *Argulus coregoni* in rainbow trout, as well as for the treatment of *Salmincola edwardsii* in brook trout. Interestingly, the observed efficacy of SLICE® against these *A. coregoni* and *S. edwardsii* included the “extended period of protection” previously documented with respect to the use of SLICE® against sea lice. It is anticipated that SLICE® may be similarly effective for the treatment of other freshwater copepods including *Actheres ambloplitis*, *Ergasilus*, and *Lernaea*. The addition of SLICE® for the control of external parasites in freshwater fish to aquaculture’s approved medicine chest would be a value-added tool to help optimize overall fish health and population fitness.

The purpose of this compassionate INAD for emamectin benzoate (SLICE®) administered in feed is to develop clinical field trial data that will be used to determine the efficacy and appropriate treatment regimens for emamectin benzoate (SLICE®) medicated feed to control mortality caused by external parasites in a variety of freshwater fish species. These data will be used to support a new animal drug application (NADA) for emamectin benzoate (SLICE®) medicated feed. The USFWS anticipates that it may take several year to complete all technical section data for a NADA for emamectin benzoate (SLICE®) medicated feed. The USFWS is aware that opportunities for emamectin benzoate (SLICE®) medicated feed therapy are unpredictable. There is no way of knowing in advance if, when, or where opportunities for pivotal studies will be encountered. The USFWS believes it is likely that data from 3-5 treatment seasons will be required in order to adequately assess the efficacy of emamectin benzoate (SLICE®) medicated feed treatment, and to generate sufficient data to support a NADA.

VI. SPECIFIC OBJECTIVES

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

1. Collect scientific data necessary to establish the efficacy of SLICE® (emamectin benzoate) administered in feed to control mortality caused by external parasites in a variety of freshwater fish species.
2. Provide the opportunity for fishery biologists to legally use SLICE® (emamectin benzoate) medicated feed to control mortality caused by external parasites in a variety of freshwater fish species during the period of time necessary for collection of efficacy, safety, and residue data required for an NADA for SLICE® (emamectin benzoate) medicated feed use in fish. Specifically, SLICE® (emamectin benzoate) medicated feed will be used in a variety of environmental conditions, at a wide range of temperatures, and in a variety of cultured fish species to maintain healthy stocks of fish during the period of time necessary for

collection of data that will be used to support an NADA for the use SLICE® (emamectin benzoate) medicated feed.

VII. MATERIALS

A. Test and control articles:

1. Drug Identity

a. Active ingredient

Common Name:	Emamectin benzoate
Product Name:	SLICE® Premix (Emamectin benzoate, 0.2% Aquaculture premix)
Chemical Name:	4"-deoxy-4"-epi-methylamino-avermectin benzoate
CAS Number:	137512-74-4
Appearance:	white to grey powder
Odor:	slight to none

- b. Strength and dosage form Emamectin benzoate is the active component of SLICE®. Emamectin is an avermectin developed initially for food crop use. Emamectin is derived synthetically from avermectins, which are produced by fermentation of the soil organism *Streptomyces avermitilis*. SLICE® Aquaculture Premix consists of 0.2% emamectin benzoate in an inert carrier, consisting of GM-free cornstarch, maltodextrin, antioxidant, and solvent. The premix has been formulated specifically for incorporation of emamectin benzoate onto fish feeds.

c. Manufacturer, source of supply

Merck Animal Health
35500 W. 91st Street
Desoto, KS 66018

Contact Person at Merck Animal Health:

Jackie Zimmerman
Phone: (208) 603-0336

email: jacqueline.zimmerman@merck.com

or

Merck Animal Health Customer Service
Phone: 1-800-521-5767
email: Customerservice@merck.com

2. Verification of drug Integrity/Strength:

The manufacturer, Merck Animal Health, will provide the analytical data necessary to establish the purity of each lot of SLICE® (emamectin benzoate) premix supplied. The lot number and date of manufacture for each batch of SLICE® (emamectin benzoate) premix 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 SLICE-1) will clearly identify the lot number and date of manufacture of SLICE® (emamectin benzoate) shipments (i.e., premix or medicated feed). If the integrity of the SLICE® (emamectin benzoate) is compromised (i.e., by spilling or contamination of the stock container or feed bags) the event will be carefully recorded, dated, and signed in the Chemical Use Log (Form SLICE-2a and/or Form SLICE-2b). The Study Monitor assigned to the Investigator involved will be immediately notified.

Based on discussions with Investigators concerning planned feed rate and kg of fish to be medicated, commercial fish feed manufacturers shall prepare feed with dosages of SLICE® (emamectin benzoate) premix to assure the target dose of 50 ug emamectin benzoate/kg fish/day is being achieved.

The Investigator may also prepare his/her own drug-treated feed by top-coating feed on-hand (or specially ordered feed) with SLICE® (emamectin benzoate) premix. Target dosage must be 50 ug emamectin benzoate/kg fish/day. If the Investigator chooses this option, they are encouraged (but not required) to have a sample of the top-coated feed assayed for emamectin benzoate concentration by a certified, analytical testing laboratory. Results of drug-treated feed assays should be appended to Form SLICE-3.

3. Storage Conditions

SLICE® (emamectin benzoate) will be stored in the original container supplied by the Manufacturer with the appropriate investigational label attached. The container will be stored in dry conditions at temperatures between 2 and 30°C. Unopened SLICE® premix stored in this manner has a shelf life of 24 months. The storage unit for SLICE® premix must be labeled to indicate that it contains hazardous material and that "*NO Food or Drink is to be Stored in this unit*". SLICE® medicated feed should be stored at temperatures and for periods of time not to exceed limits set by the feed manufacturer.

Medicated feed should be ordered only as needed and not stored for possible future use.

4. Handling Procedures

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

5. Investigational Labeling

A copy of the label to be attached to each container of SLICE® (emamectin benzoate) and all bags of SLICE® (emamectin benzoate) medicated feed are provided in Appendix V. It is the responsibility of the Investigator to ensure proper labeling of all containers of SLICE® (emamectin benzoate) premix and medicated feed.

6. Accountability

Merck Animal Health will be the sole supplier of SLICE® (emamectin benzoate) to all Investigators under INAD 11-370.

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 SLICE® (emamectin benzoate) medicated feed:

Immediately upon receiving an order/shipment of SLICE® premix or SLICE® (emamectin benzoate) medicated feed, the Investigator must complete Form SLICE-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 SLICE-1s are received by the Study Director within 10 days of drug receipt.

All Investigators are also responsible for maintaining an accurate inventory of SLICE® (emamectin benzoate) medicated feed on-hand. A Chemical Use Log

(Form SLICE-2a or SLICE-2b) must be completed and maintained by each Investigator. Each time SLICE® (emamectin benzoate) medicated feed 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 SLICE® (emamectin benzoate) or SLICE® (emamectin benzoate) medicated feed will be destroyed by following the SDS (note: unless SLICE® (emamectin benzoate) medicated feed is planned for use in another approved field trial, and planned usage is within the storage guidelines established by the manufacturer). Disposition of all SLICE® (emamectin benzoate) or SLICE® (emamectin benzoate) medicated feed must be properly recorded and accounted for on the Chemical Use Log (Form SLICE-2a or SLICE 2b). The Study Monitor will be responsible for verifying the quantity of SLICE® (emamectin benzoate) or SLICE® (emamectin benzoate) medicated feed remaining on hand versus the amount indicated on Form SLICE-2a or SLICE 2b. **Note:** SLICE® (emamectin benzoate) or SLICE® (emamectin benzoate) medicated feed can be transferred to other facilities that are participating under INAD 11-370. Transfers must be shown in the Drug Inventory section of the database (formerly Form SLICE-2a or SLICE-2b).

7. Preparation Procedures

SLICE® (emamectin benzoate) will be supplied to Investigators either as SLICE® premix or as SLICE® medicated feed. Neither product should be adulterated in any manner prior to use. If Investigators are using SLICE® premix to make their own SLICE® medicated feed, SLICE® premix should be top-coated on feed. Top-coating procedures should include “finishing” with 0.5% vegetable oil.

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 fish and identify parasites.

When the Study Protocol has been approved and treatments are scheduled, the Investigator at each facility covered by the SLICE® (emamectin benzoate) medicated feed 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 these clinical field trials will consist of contained or isolated groups of fish. This will generally be a groups of fish contained in tanks, raceways, or ponds. However, the experimental unit in clinical field trials may also be **individual animals**. If individual animals are

considered to be the experimental unit, treatment response parameters for each animal must be evaluated separately.

IX. ENTRANCE CRITERIA

A. Facilities/Investigators

It is important to note that all facilities need to be approved by the FDA/CVM Environmental Team prior to participation in the INAD. If any of the approved conditions (i.e., number of treated fish; number of treatments each year; discharge of treated water; etc...) changes at your facility then a new approval will be required before new treatments can begin. The proposed facility and the Investigator must be listed in Appendix IIIa of the Study Protocol for the current calendar year before SLICE® (emamectin benzoate) medicated feed 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 Form SLICE-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 SLICE-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 SLICE-2a or SLICE-2b and SLICE-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.

A. Pathogen/disease considerations

1. Parasites 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 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 Form 3 "Diagnosis and Treatment Record"**). There should be increased mortality rates among fish in two or more similar rearing units 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.)

2. Typical disease signs should be detectable in at least a few fish and the causative parasite must be identified.

3. Prophylactic Treatment:

Prophylactic (preventative) treatment of fish with SLICE® (emamectin benzoate) medicated feed **will not be allowed** under this INAD exemption.

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. Separately confined, untreated control fish will not be required in supplementary field studies conducted to determine the effectiveness of SLICE® (emamectin benzoate) medicated feed treatment. Fish from a group or lot will first be examined to determine if treatment with SLICE® (emamectin benzoate) is required. When treatment is underway or has been completed, fish from the same group will be examined to determine the effect of treatment on the parameters used to initially sanction the treatment. Evaluation will in all cases consist of determining fish mortality, although in most cases degree or severity of parasite infestation will also be quantified.
- 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 SLICE® (emamectin benzoate). 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

SLICE® (emamectin benzoate) will be administered only as a medicated feed treatment.

B. Dose to be administered

SLICE® (emamectin benzoate) will be administered at a dosage of 50 ug/kg of fish biomass/day.

C. Dosing interval and repetition

SLICE® (emamectin benzoate) will be administered as a single treatment regimen, with no repetition of treatment.

D. Duration of treatment

SLICE® (emamectin benzoate) medicated feed will be fed for 7 consecutive days.

E. Drug preparation and administration procedures

SLICE® (emamectin benzoate) premix will typically be incorporated into standard diets by an established feed manufacturer. However, in certain situations, SLICE® (emamectin benzoate) premix may be top-coated on feed by investigators. Standard personal protective equipment such as gloves, lab coats or aprons, eye protection, etc. should be worn at all times when preparing or administering SLICE® (emamectin benzoate) medicated feed. Medicated feed for each individual lot of fish should be accurately weighed prior to treatment. Fish should be fed in such a manner as to ensure optimal consumption of SLICE® (emamectin benzoate) medicated feed (see Feeding regimen below).

B. Feeding regimen

During the course of therapy fish may be fed only treated feed, or a combination of treated and untreated feed. The actual feeding regimen used will be left to the discretion of the investigator, and will be dictated by the feeding behavior of the fish to be treated and level of premix incorporated in the feed. In most cases it is anticipated that use of only treated feed will work best. However, in some cases, treated feed followed by untreated feed may be determined to be the optimal feeding regimen. In still other cases, a small amount of untreated feed followed by a “full course” of treated feed may be utilized. In all cases, the daily feeding regimen should be designed to maximize consumption of the treated feed to result in the intended dosage of 50 ug emamectin benzoate per kg body weight.

Specify on source data sheets how fish were fed (e.g. % treated feed vs % untreated feed, by hand, using automatic feeders, utilizing demand feeders), amount of feed offered (% body weight), and whether feed was well accepted or poorly utilized.

G. Permissible concomitant therapy

Since efficacy data are being collected during the INAD process, there should be 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 SLICE® (emamectin benzoate) medicated feed.

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 SLICE® (emamectin benzoate) medicated feed treatment involved should be appropriately labeled. Contact the AADAP Office for the information that will need to be provided in the Form SLICE-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 other pertinent species information indicating 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 SLICE-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 parasite load, usually indicate when SLICE® (emamectin benzoate) medicated feed treatment is needed. **This source data must be collected for at least 5 days before treatment, during treatment, and for up to at least 10 days after the treatment period has ended.** Collection of this data is critically important in all cases. Gill, skin, fin, mucous or other tissue from groups of representative fish should be evaluated using appropriate methodology to determine parasite presence and load (i.e., parasite density).

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 SLICE® (emamectin benzoate) medicated feed has been used fairly extensively with beneficial effect in fish culture, and is currently approved in the UK, Ireland, Norway, Chile, and Canada, it is possible adverse reactions may occur under certain environmental conditions or with respect to specific species/strains of fish. Investigators should carefully observe all treated fish for any signs of adverse reaction to treatment. The Investigator should carefully document all observations of adverse reactions on Form SLICE-3. **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 the SLICE® (emamectin benzoate) medicated feed INAD will need to complete the following forms:

Form SLICE-W.	Worksheet for Designing Individual Field Trials under INAD 11-370 - located in the New Study Request tab
Form SLICE-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 SLICE-2a.	Chemical Use Log for Clinical Field Trials Using SLICE® (emamectin benzoate) Medicated Feed under INAD 11-370 - <u>SLICE® Premix</u> – located in the Manage/View Drug Inventory tab and filled out in Form SLICE-3 to show use
Form SLICE-2b.	Chemical Use Log for Clinical Field Trials Using SLICE® (emamectin benzoate) Medicated Feed under INAD 11-370 - <u>SLICE® Medicated Feed</u> – located in the Manage/View Drug Inventory tab and filled out in Form SLICE-3 to show use
Form SLICE-3.	Results Report Form for use of SLICE® (emamectin benzoate) under INAD 11-370 – located in the Active Studies table on the home page
Form SLICE-3s	Supplemental Information Documenting Level of Parasite Infestation Pre-Treatment and Post-Treatment – located in Form SLICE-3

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 SLICE® (emamectin benzoate) medicated feed must be maintained in culture facilities for a **minimum of 60 days** following completion of therapy before stocking/release or harvest.

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

XVI. DISPOSITION OF INVESTIGATIONAL DRUG

SLICE® (emamectin benzoate) medicated feed will be used only in the manner and by the individuals specified in the Study Protocol. If any unused or outdated SLICE® (emamectin benzoate) medicated feed 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 SLICE® (emamectin benzoate) or SLICE® (emamectin benzoate) medicated feed must be properly recorded and accounted for on the Chemical Use Log (Form SLICE-2a or SLICE-2b). The Study Monitor will be responsible for verifying the quantity of SLICE® (emamectin benzoate) or SLICE® (emamectin benzoate) medicated feed remaining on hand versus the amount indicated on Form SLICE-2a or SLICE-2b. 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 SLICE® (emamectin benzoate) medicated feed is planned for use in another approved field trial, and planned usage is within the storage guidelines established by the manufacturer).

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 SLICE® (emamectin benzoate) medicated feed 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 SLICE[®] (emamectin benzoate) medicated feed 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

SLICE[®] (emamectin benzoate) medicated feed will be administered directly by the assigned Investigator (fish hatchery manager) or under the Investigator's direct supervision (see Appendix IIIa for names). SLICE[®] (emamectin benzoate) medicated feed 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 protocol Section VII.A.6. Accountability for details and the following forms will be used as guides for data collection: Form SLICE-W, Form SLICE-1, Form SLICE-2a, Form SLICE-2b, Form SLICE-3, and Form SLICE-3s.

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 trials 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 forwarded to 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 out 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 SLICE-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.

LITERATURE CITED

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- Dunston, J. and R.R. Cusak. 2002. Emamectin benzoate: an effective in-feed treatment against the gill parasite *Salmincola edwardsii* on brook trout. Aquaculture. 207: 1-9.
- Hakalahti, T, Y. Lankinen, and E.T. Valtonen. 2004. Efficacy of emamectin benzoate in the control of *Argulus coregoni* (Crustacea:Branchiura) on rainbow trout *Oncorhynchus mykiss*. Diseases of Organisms. 60: 187-204.
- Roy, W.J., I.H. Sutherland, H.D.M. Roger, and K.J. Varma. 2000. Tolerance of Atlantic salmon, *Salmo salar* L., and rainbow trout, *Oncorhynchus mykiss* (Walbaum), to emamectin benzoate, a new orally administered treatment for sea lice. Aquaculture. 184: 19-29.
- Stone, J., I.H. Sutherland, C. Sommerville, R.H. Richards, and K.J. Varma. 1999. The efficacy of emamectin benzoate as an oral treatment of sea lice, *Lepeophtheirus salmonis* (Kroyer), infestations in Atlantic salmon, *Salmo salar* L. Journal of Fish Diseases. 22: 261-270.
- Stone, J., I.H. Sutherland, C. Sommerville, R.H. Richards, and K.J. Varma. 2000a. Field trials to evaluate the efficacy of emamectin benzoate as an oral treatment of sea lice, *Lepeophtheirus salmonis* (Kroyer), and *Caligus elongatus* Nordman, infestations in Atlantic salmon, *Salmo salar* L. Aquaculture. 186: 205-219.
- Stone, J., I.H. Sutherland, C. Sommerville, R.H. Richards, and K.J. Varma. 2000b. Commercial trials using emamectin benzoate to control *Lepeophtheirus salmonis* (Kroyer), and *Caligus elongatus* Nordman, infestations in Atlantic salmon, *Salmo salar* L. Diseases of Aquatic Organisms. 41: 141-149.
- Stone, J., I.H. Sutherland, C. Sommerville, R.H. Richards, and R.G. Endris. 2000c. The duration of efficacy following oral treatment with emamectin benzoate against infestations of sea lice, *Lepeophtheirus salmonis* (Kroyer) in Atlantic salmon, *Salmo salar* L. Journal of Fish Diseases. 23:185-192.
- Stone, J., W.J. Roy, I.H. Sutherland, H.W. Ferguson, C. Sommerville, R.H. Richard, and R.G. Endris. 2002. Safety and efficacy of emamectin benzoate administered in feed to Atlantic salmon, *Salmo salar* L., smolts in freshwater, as a preventative treatment against infestations of sea lice, *Lepeophtheirus salmonis* (Kroyer). Aquaculture. 210: 21-34.

Appendix I. Sponsor Contact Information for SLICE[®] (EMAMECTIN BENZOATE) INAD #11-370

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

¹Appendix II. Study Monitors for SLICE[®] (EMAMECTIN BENZOATE) INAD #11-370

Note: This information will be provided directly to CVM

1Appendix IIIa. Facilities and Names of Investigators Participating under SLICE® (EMAMECTIN BENZOATE) INAD #11-370

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.

Appendix IV. Safety Data Sheet (SDS) for SLICE[®] (EMAMECTIN BENZOATE) INAD #11-370

The SDS for SLICE[®] can be found at the drug supplier's website

[Emamectin Formulation_AH_US_EN.pdf \(merck.com\)](#)

1

Appendix V. Investigational Label for SLICE® (EMAMECTIN BENZOATE) INAD #11-370

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 SLICE®
(EMAMECTIN BENZOATE) INAD #11-370**

Freshwater fish
Marine fish

1

**Appendix VIb. Table of Facilities and Fish Stocks Treated
under SLICE[®] (EMAMECTIN BENZOATE) INAD #11-370**

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 database. Any paper forms that are submitted to AADAP will be sent back to the study participants.

Form SLICE-W: Worksheet for Designing Individual Field Trials Under SLICE® (Emamectin Benzoate) INAD 11-370

INSTRUCTIONS

1. Investigator must fill out Form SLICE-W for each trial conducted under this INAD **before** actual use of SLICE® medicated feed.
2. Investigator should forward a copy of SLICE-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 parasite to be treated			
Fish species/stock to be treated			
Number of fish per rearing unit (i.e., tank, raceway, or pond)			
Number of rearing units to be treated		Number of untreated (i.e., control) rearing units	
Average number of fish per pound		Estimated total weight of treated fish (lbs)	
Intended SLICE® (emamectin benzoate) dosage	50 ug per kg per day		
Feed rate (% body weight to be fed per day)			
Planned duration of treatment (days)	7		
Estimated amount of medicated feed needed for proposed treatment (lbs or kg)			
Anticipated date treatment will be initiated			

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):

☐ Investigator should initial here to indicate awareness that fish disposition must be in compliance with the FDA-mandated withdrawal time of 60 days as described in the Study Protocol.

**USE AND DISPOSITION OF EMAMECTIN BENZOATE (SLICE®)
MEDICATED FEED (Environmental Safety Considerations):**

☐ Investigator should initial here to indicate awareness that SLICE® (emamectin benzoate) medicated feed usage and disposition must be in compliance with requirements described in the Study Protocol.

WORKER SAFETY CONSIDERATIONS:

☐ Investigator should initial here to indicate that all personnel handling SLICE® (emamectin benzoate) medicated feed have read the Safety Data Sheet for SLICE® (emamectin benzoate) premix and have been provided personal protective equipment, in good working condition, as described in the Study Protocol.

**Date
Prepared:** _____

Investigator: _____

Date
Reviewed:

Study Monitor:

FORM SLICE-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 SLICE-1 **immediately** upon receipt of SLICE® medicated feed.
2. Investigator should forward a copy of Form SLICE-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	SLICE® (Emamectin benzoate)	INAD Number	11-370
Proposed Use of Drug	Treatment of external parasites that occur in a variety of freshwater fish species		
Date of CVM Authorization Letter	07/15/2020		
Date of Drug Receipt		Amount of Drug Received	
Drug Lot Number		Trial Number	
Name of Investigator			
Address of Investigator			
Location of Trial			
Pivotal Study	Yes	Non-pivotal Study	----
Approximate Number of Treated Animals		Approximate Number of Control Animals	
Number of Animals Used Previously ¹			
Study Protocol Number	11-370		
Approximate dates of trial (start/end)			
Species, Size, and Type of Animals			
Maximum daily dose and duration	50 ug emamectin benzoate / kg fish / day for 7 days		
Methods(s) of Administration	Medicated-feed		
Withdrawal Period	60 days - all species		

¹ To be filled out by the AADAP Office

Date Prepared: _____

Investigator: _____

Date Reviewed: _____

Study Monitor: _____

Date Reviewed:

Study Director:

Instructions:

1. Initiate Form 2a immediately upon receipt of SLICE® (emamectin benzoate) premix.
2. Each lot number of SLICE® (emamectin benzoate) premix may be used for multiple treatment regimens.

From Previous Page (g):

Facility:

Reporting Individual:[illegible]

¹ Unused SLICE® Premix that is shipped to another facility participating in SLICE® INAD #11-370 (Note: SLICE® Premix can only be shipped to another facility with prior authorization by the AADAP Office).

² Unused SLICE® Premix that is disposed of by burial or in a landfill.

Investigator: _____
Signature and Date _____

Study Monitor: _____
Signature and Date

Form SLICE-2b. Chemical Use Log for Clinical Field Trials Using SLICE® (emamectin benzoate) Medicated Feed Under INAD #11-370 - SLICE® Medicated Feed

- Instructions:**
1. Initiate Form 2b immediately upon receipt of SLICE® (emamectin benzoate) medicated feed.
 2. Each lot number of SLICE® (emamectin benzoate) medicated feed should be used for a single treatment regimen.

Quantity on Hand

From Previous Page (lbs):

Facility:

Reporting
Individual:

SLICE® Medicated Feed Lot Number	Date Received	Amount Received (lbs)	Dates Used	Study Number	SLICE® Medicated Feed Used for Treatment (lbs)	SLICE® Medicated Feed Shipped ¹ (lbs)	SLICE® Medicated Feed Disposal ² (lbs)	SLICE® Medicated Feed On-hand (lbs)	Inventoried by (initials)

¹ Unused SLICE® medicated feed that is shipped to another facility participating in SLICE® INAD #11-370 (Note: SLICE® medicated feed can only be shipped to another facility with prior authorization by the AADAP Office).

² Unused SLICE® medicated feed that is disposed of by burial or in a landfill.

Investigator: _____
Signature and Date

Study Monitor: _____
Signature and Date

1STUDY NUMBER _____

Page 1 of 5

Form SLICE-3: Results Report Form for Clinical Field Trials Using SLICE® (emamectin benzoate) Medicated Feed Under INAD 11-370

INSTRUCTIONS

- Investigator must fill out Form SLICE-3 no later than 30 days after completion of treatment. Attach lab reports and other information.
- If SLICE® (emamectin benzoate) was not used under the assigned Study Number, contact the Study Director at the AADAP Office on how to close-out the study.
- Investigator should forward a copy of Form SLICE-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	

FISH CULTURE AND DRUG TREATMENT INFORMATION

SLICE® (emamectin benzoate) lot number		Medicated feed manufacture/preparation date	
Treatment dosage	50 ug/kg bw/day	Treatment duration	7 days
Fish species treated		Fish parasite treated	
Number of rearing units treated		Number of fish per treated rearing unit	
ID of all treated rearing units (e.g. Tank 5, Pond 6B)			
Total number of fish treated			
Number of control units		Number of fish per control unit	
Number of fish per pound		Average fish length (in)	
Preparation of medicated feed (i.e. top-coated at your facility or prepared by feed manufacturer)			
Feed type (manufacturer, moist <u>vs</u> dry, particle size)			
Feed rate (% BW fed per day)			
Date treatment initiated		Date treatment completed	

OMB Control No. 1018-New

Expires ##/##/20##

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 Treated or Control, and the number of fish in each rearing unit.
3. Water temperature and individual tank mortality should be recorded on a daily basis.
4. **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									
	5									
	6									
	7									
Post-treatment period	1									
	2									
	3									
	4									
	5									
	6									
	7									
	8									
	9									
	10									

WATER QUALITY PARAMETERS

Ave pre-treatment temp (°F)		Dissolved Oxygen (mg/L)	
Ave treatment temp (°F)		pH	
Ave post-treatment temp (°F)		Hardness - CaCO ₃ (mg/L)	

RESULTS: Describe in detail treatment results. Was treatment successful? If treatment did not appear to be successful, explain why not? Describe general fish behavior, including feeding behavior. 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:

Observed withdrawal
period:

60 days

Investigator should initial here to indicate compliance with established withdrawal period

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

DISPOSITION OF SLICE® (EMAMECTIN BENZOATE) MEDICATED FEED

	Use and disposition of all SLICE® (emamectin benzoate) medicated feed followed Study Protocol guidelines and has been clearly identified on Form SLICE-2b (Investigator should initial)
	NEGATIVE REPORT: SLICE® (emamectin benzoate) medicated feed 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: _____

STUDY NUMBER: _____

Page 1 of 2

Form SLICE-3s: Supplemental Information Documenting Level of Parasite Infestation Pre-Treatment and Post-Treatment**INSTRUCTIONS**

1. Investigator should fill-out one copy of Form SLICE-3s for each rearing unit treated.
2. Be sure to include STUDY NUMBER in upper left-hand corner of this form.
3. Data on Pre-treatment level of infestation should be collected within 5 days prior to the initiation of treatment.
4. Data on Post-treatment level of infestation should be collected at least once.
5. Note: Each sampling (i.e., pre- and post-treatment) should include data from a minimum of 10 fish, and completed Form SLICE-3s's should be appended to Form SLICE-3.

Rearing Unit ID: _____

Pre-treatment		
Date	Fish Number	Number of Parasites
	1	
	2	
	3	
	4	
	5	
	6	
	7	
	8	
	9	
	10	
	11	
	12	
	13	
	14	
	15	
	16	
	17	
	18	
	19	
	20	
	21	
	22	
	23	
	24	
	25	
	26	
	27	
	28	
	29	
	30	

¹ Additional copies of

Post-treatment ¹			
Date	Days Post-treatment	Fish Number	Number of Parasites
		1	
		2	
		3	
		4	
		5	
		6	
		7	
		8	
		9	
		10	
		11	
		12	
		13	
		14	
		15	
		16	
		17	
		18	
		19	
		20	
		21	
		22	
		23	
		24	
		25	
		26	
		27	
		28	
		29	
		30	

table
for
post-

treatment infestation level are

available on page 2 of this form

Form SLICE-3s: Supplemental Information Documenting Level of Parasite Infestation

STUDY NUMBER: _____

Page 2 of 2

Additional Documentation of Level of Parasite Infestation Post-Treatment

Rearing Unit ID: _____

Post-treatment			
Date	Days Post-treatment	Fish Number	Number of Parasites
		1	
		2	
		3	
		4	
		5	
		6	
		7	
		8	
		9	
		10	
		11	
		12	
		13	
		14	
		15	
		16	
		17	
		18	
		19	
		20	
		21	
		22	
		23	
		24	
		25	
		26	
		27	
		28	
		29	
		30	

Post-treatment			
Date	Days Post-treatment	Fish Number	Number of Parasites
		1	
		2	
		3	
		4	
		5	
		6	
		7	
		8	
		9	
		10	
		11	
		12	
		13	
		14	
		15	
		16	
		17	
		18	
		19	
		20	
		21	
		22	
		23	
		24	
		25	
		26	
		27	
		28	
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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 5 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].