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:

Intervet/Schering-Plough Animal Health
56 Livingston Avenue
Roseland, NJ 07068

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	April 30, 2014
Study Director	Mr. Jim Bowker

_____ _____

Study Director Signature Date

Clinical Field Trial Location and Trial Number:

_____ _____

Type or Print Facility Name Trial Number

Investigator_____

Type or Print Name

_____ _____

Investigator Signature Date

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

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

Manufacturer: Intervet/Schering-Plough Animal Health
56 Livingston Avenue
Roseland, NJ 07068

Contact: Richard Endris; Phone: 862-245-5133

Study Director: Mr. Jim Bowker, U.S. Fish and Wildlife Service, Aquatic Animal Drug Approval Partnership (AADAP) Program, 4050 Bridger Canyon Road, Bozeman, MT 59715; Phone: 406-994-9910; Fax: 406-582-0242; Email: jim_bowker@fws.gov

Principal Clinical Field Trial Coordinator: Bonnie Johnson, USFWS - AADAP

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

III. INVESTIGATORS/FACILITIES

See Appendix IIIa for names and addresses.

IV. PROPOSED STARTING AND COMPLETION DATES:

Proposed Starting Date: May 1, 2010

Proposed Completion Date: April 30, 2014

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 (*Icthyopthirius, 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 or 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 regimes 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

Intervet/Schering-Plough Animal Health
56 Livingston Avenue
Roseland, NJ 07068

Contact Person: Richard Endris
Phone: 862-245-5133
Fax: 862-245-3654

2. Verification of drug integrity/strength:

The Manufacturer, Intervet/Schering-Plough 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 benzoatel/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 benzoatel/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^{o}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 Material Safety Data Sheet (MSDS) 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 MSDS. Safety precautions as outlined in the MSDS will be followed at all times when working with SLICE® (emamectin benzoate).

5. Investigational labeling

Copies of the labels 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

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

1. USFWS and Non-USFWS Facilities

Immediately upon receiving an order/shipment of SLICE® (emamectin benzoate), the Investigator will complete Form SLICE-1 "Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals". The investigator will archive the original in the facilities INAD file, and send a copy to his/her Study Monitor. Both the Investigator and the Study Monitor are required to sign Form SLICE-1. The Study Monitor will then forward a copy to the Clinical field Trial Coordinator at the Aquatic Animal Drug Approval Partnership Office. The Clinical Field Trial Coordinator will archive one copy, and send two copies of Form SLICE-1 to FDA. Arrangements should be made between Investigators and Study Monitors to insure completed Form SLICE-1s are received by the Clinical field Trial Coordinator in a timely manner.

All Investigators are also responsible for maintaining an accurate inventory of SLICE® (emamectin benzoate) on-hand. A Chemical Use Log (Forms SLICE-2a and SLICE-2b) will be supplied to each Investigator. Each time SLICE® (emamectin benzoate) is used, it must be recorded by the Investigator on Form SLICE-2a and/or Form 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) INAD will need to complete several forms. These forms are described in Section XIII (p 11). Copies of these forms are attached to this Study Protocol.

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

The proposed facility and the Investigator must be listed in Appendix IIIa of the Study Protocol 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).

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.

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).

E. 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").

2. 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.)

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

4. Since the efficacy of SLICE® (emamectin benzoate) medicated feed therapy for the control of a external parasites is being tested, investigators must be prepared to make no changes in the fish cultural procedures or environmental conditions and apply no other treatments once a decision has been made to conduct SLICE® (emamectin benzoate) medicated feed therapy. Complicating bacterial or other parasitic diseases should be carefully documented. If necessary, these infections can be treated once SLICE® (emamectin benzoate) medicated feed response (efficacy) data has been collected. However, it may take as long as 10 days after the completion of SLICE® (emamectin benzoate) medicated feed therapy to determine differences between test and control groups and to complete post-treatment evaluations.

Prior to initiating each treatment event, the Investigator must first complete Form SLICE-W. "Worksheet for Designing Individual Field Trials" that pertains to each specific treatment event. The worksheet should be filled out, signed, and sent by Fax to the Study Monitor. The Study Monitor will review the planned treatment (worksheet), sign it, and forward (Fax) the paperwork to the AADAP Office. The AADAP Office will then review the worksheet, assign the approved treatment a Study Number, and then 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 Form SLICE-2a (and/or Form 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 his/her Study Monitor with regards to worksheet approval, and infection/disease/treatment need is rapidly escalating, the Investigator should contact the AADAP Office for a study number and permission to proceed.

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.

Although untreated control groups are not a required element of treatment under this INAD exemption and are at the discretion of the Investigator, they are strongly encouraged whenever circumstances permit. Control groups are extremely important to not only document response to treatment, but also to validate potential adverse reactions in treated animals. Use of control groups will ensure that results of efficacy studies provide useful information that will support an NADA.
It is important that all fish are treated in a similar fashion. If fish are physically moved into separate test groups or different rearing units, caution should be used so that handling and rearing conditions are as similar as possible. Control fish should be kept under conditions as similar as possible to treated fish for valid comparison. Although not required, replicate treatment groups are strongly encouraged in both treated and control groups. Assignment to control and treatment groups should be random and designed to avoid bias.

Blinded studies can reduce bias in data collection. Whenever possible, investigators should consider methods by which treatment response observations are recorded by individuals who are unaware which fish have been treated and which fish are controls.

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 regime, 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 Regime below).

F. Feeding Regime

During the course of therapy fish may be fed only treated feed, or a combination of treated and untreated feed. The actual feeding regime 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 regime. 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 regime 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 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 make no changes in fish cultural procedures or environmental conditions, and apply no other drug therapy once a decision has been made to conduct SLICE® (emamectin benzoate) medicated feed treatment. However, if concomitant therapy is required in order to protect valuable fish stocks, it should be fully documented and the efficacy data from the SLICE® (emamectin benzoate) medicated feed treatment involved should be appropriately labeled.

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. 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 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
Form SLICE-1.	Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals
Form SLICE-2a.	Chemical Use Log for Clinical Field Trials Using SLICE® (emamectin benzoate) Medicated Feed under INAD 11-370 - SLICE® Premix
Form SLICE-2b.	Chemical Use Log for Clinical Field Trials Using SLICE® (emamectin benzoate) Medicated Feed under INAD 11-370 - SLICE® Medicated Feed

Form SLICE-3. Results Report Form for use of SLICE® (emamectin benzoate) under INAD 11-370

Copies of these forms are attached to this Study Protocol.

XIV. RECORD KEEPING PROCEDURES

The data should be recorded in permanent ink (preferably black). The data should be recorded on the official data record forms at the time the observations are made. The raw data should be original, i.e., they should be the first recording of the observations, rather than a transcription of original observations to another data sheet. Each original data sheet should be legibly signed and dated by the person making the observation and recording the entry. If more than one person makes and records the observations, entries should be properly attributed to each person. The data should be accurate and legible. If a mistake is made, it should be crossed out using a single strike-through and the correct data should be recorded next to it. Each change to the raw data should be initialed and dated by the person making the change, and a statement should be provided explaining why the change was made. If the data sheet needs to be copied, all data should be transferred, including the properly noted changes. The original record should be retained and submitted with the revised copy, along with a memo explaining the reason for the copying.

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.

No withdrawal period will be required for fish that will not be catchable for 60 or more days after release or are illegal for harvest during that 60 day period. No withdrawal period shall be required for dead fish that will be buried or rendered into non-edible products.

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 out-dated SLICE® (emamectin benzoate) medicated feed remains at the end of the study period, Investigators should contact Study Monitors for instructions regarding drug disposal.

The investigational drug may not be redistributed to others not specified in the Study Protocol.

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

A. Drug distribution

See Section VII.A.6. Accountability (page 6) 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 should be assigned to each facility that is authorized to treat fish with SLICE® (emamectin benzoate) medicated feed. 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., page 6).

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 Section VII.A.6. Accountability (page 6) for details and Forms SLICE-W, SLICE-1, SLICE-2a, SLICE-2b, and SLICE-3 (page 11) for actual forms to be used in the study.

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 Monitors who will review the information and ensure that all required data 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 an annual report that will be submitted to the FDA.

G. Data storage

The Investigator is responsible for complete and accurate data collection. The Investigator is also responsible for archiving a complete set of all original data. A copy of Form SLICE-1 should be sent immediately to the Study Monitor, who will in turn forward a copy to the Study Director. A copy of Form SLICE-2 should be sent to Study Monitors with the corresponding Form SLICE-3 (if no further treatments are necessary/planned), or at the end of the calendar year. A copy of Form SLICE-3 should be sent to the Study Monitor after completion of the entire treatment period, which includes the post-treatment observation period. Study Monitors should carefully check each set of data for accuracy and completeness. If there are any discrepancies in the data, the Study Monitor should contact the Investigator immediately to rectify the problem. After review, Study Monitors should forward all data to the Study Director. As stated above, a complete set of raw data should be archived by the Investigator. All data should be stored in a secure place. Another complete data set (copies) will be archived by the Study Director.

XVIII. PLANS FOR DATA ANALYSIS

Data analysis will be completed by the Study Director located at the Bozeman National INAD Office. Data from the treatment year will be summarized through tabulation and appropriate statistical analysis. An annual report will be prepared and submitted to the FDA. This submission will probably 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 the study 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**. Deviation statements should be signed and dated. These statements should be forwarded to the Study Monitor along with Form SLICE-3, and ultimately be submitted to the Study Director.

LITERATURE CITED

Armstrong, R., D. MacPhee, T. Katz, and R. Endris. 2000. A field efficacy evaluation of emamectin benzoate for the control of sea lice in Atlantic salmon. Canadian Veterinary Journal. 41: 607-612.

Dunston, J. and R.R. Cusak. 2002. Emamcetin 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 myskiss*. 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, *Slamo 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 treatmentof 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 ememectin 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 is freshwater, as a preventative treatment against infestations of sea lice, *Lepeophtheirus salmonis* (Kroyer). Aquaculture. 210: 21-34.

SAFETY DATA SHEET

1 PRODUCT AND COMPANY IDENTIFICATION

Product name: SLICE (Emamectin Benzoate 0.2% Aquaculture Premix)

SDS No: P00000023015

Synonyms, Trade Names:
SLICE Premix, SP000125

Manufacturer:
Merck
One Merck Drive P.O. Box 100
Whitehouse Station, NJ, USA 08889-0100

Telephone: 908-423-1000 (General Information Only)
Fax: 908-735-1496

Contact Person: EHS Data Steward
e-mail: MSDS@merck.com

Emergency telephone: 1-908-423-6000 (24/7/365) English Only

Intended Use: Finished veterinary product: Antiparasitic

2 HAZARDS IDENTIFICATION

Emergency Overview:

Appearance:	
Color:	White, Gray
Form :	Powder
Signal words	CAUTION!
Potential Health Effects:	
General	Finished veterinary product: Toxic if swallowed. Harmful if inhaled. Do not breathe dust or vapor. Do not eat, drink or smoke when using the product. Wash thoroughly after handling. Avoid release to the environment.
Inhalation:	Harmful if inhaled.
skin:	No data available.
eye:	No data available.
Ingestion:	Toxic if swallowed.
OSHA Regulatory Status	This product is hazardous according to OSHA 29CFR 1910.1200.
Environment:	Very toxic to aquatic life with long lasting effects.
OTHER INFORMATION	No additional information

3 COMPOSITION / INFORMATION ON INGREDIENTS

General information: The formulations for these products are proprietary information. Only hazardous ingredients in concentrations of 1% or greater and/or carcinogenic ingredients in concentrations of 0.1% or greater are listed in the composition table. Active ingredients in any concentration are listed.

Hazardous Component(s):

Chemical name	CAS-No.	Concentration
Propylene Glycol	57-55-6	2.50%
Emamectin benzoate	137512-74-4	0.20%

* All concentrations are percent by weight unless ingredient is a gas. Gas concentrations are in percent by volume.

4 FIRST AID MEASURES

Inhalation: Move into fresh air and keep at rest. For breathing difficulties, oxygen may be necessary. Get medical attention. If breathing stops, provide artificial respiration.

Skin contact: Wash skin thoroughly with soap and water. Get medical attention if irritation persists after washing. Remove contaminated clothing and shoes. Wash contaminated clothing before reuse. Destroy or thoroughly clean contaminated shoes.

Eye contact: Immediately flush with plenty of water for at least 15 minutes. If easy to do, remove contact lenses. Get medical attention.

Ingestion: Do not induce vomiting unless directed to do so by medical personnel. Never give liquid to an unconscious person. Get medical attention.

Notes to the physician:
Hazards: See Sections 2 and 11.
Treatment: Treat supportively and symptomatically.

5 FIRE-FIGHTING MEASURES

Extinguishing media: Water spray, fog, CO2, dry chemical, or alcohol resistant foam.

Unsuitable extinguishing media: None known.

Unusual Fire & Explosion Hazards: Emits toxic fumes under fire conditions.

Special Fire Fighting Procedures: Self-contained breathing apparatus and full protective clothing must be worn in case of fire.

Protective Measures: Prevent runoff from fire control or dilution from entering streams, sewers, or drinking water supply.

6 ACCIDENTAL RELEASE MEASURES

Personal precautions: Use personal protective equipment. Immediately contact emergency personnel. Keep unnecessary personnel away. Follow all fire fighting procedures.

Environmental precautions: Do not release into the environment.

Spill Cleanup Methods: Use a vacuum cleaner. If not possible, moisten dust with water before it is collected with shovel, broom or the like. Collect in containers and seal securely. For waste disposal, see section 13 of the MSDS. Prevent runoff from entering drains, sewers, or streams.

7 HANDLING AND STORAGE

Handling: Do not breathe dust. Avoid contact with eyes, skin, and clothing. Wash thoroughly after handling.

Storage: Keep container tightly closed in a cool, well-ventilated place.

8 EXPOSURE CONTROLS / PERSONAL PROTECTION

Exposure limits:

Chemical name	Type	Exposure Limit values	Source
Starch	TWA	10 mg/m3	US. ACGIH Threshold Limit Values (2009)
Starch - Respirable fraction.	PEL	5 mg/m3	US. OSHA Table Z-1 Limits for Air Contaminants (29 CFR 1910.1000) (02 2006)
Starch - Total dust.	PEL	15 mg/m3	US. OSHA Table Z-1 Limits for Air Contaminants (29 CFR 1910.1000) (02 2006)
Propylene Glycol - Aerosol.	TWA	10 mg/m3	US. Workplace Environmental Exposure Level (WEEL) Guides (2009)
Emamectin benzoate	TWA	15 ug/m3 (OEB 3)[a.]	Merck
	Wipe Limit	150 ug/100 cm2	Merck

OEB (Occupational Exposure Band) is an internal Merck control band.

a. A skin notation has been assigned to this compound because cutaneous exposure may contribute significantly to the overall exposure and produce systemic effects.

Protective Measures: Observe occupational exposure limits and minimize the risk of inhalation of dust. Minimize open handling. Containment technologies suitable for controlling compounds are required to control at source and to prevent migration of the compound to uncontrolled areas (e.g., open-face containment devices).

Respiratory Protection: Use an appropriate approved air-purifying respirator equipped with HEPA cartridges/canisters where there is the potential for exceeding established occupational exposure limits or occupational exposure bands. Powered air filter respirator. Use a positive pressure, air-supplied, pressure demand tight fitting respirator (e.g., SCBA or airline equipped with emergency escape bottle) where there is a potential for uncontrolled releases in excess of the respirator's capabilities, where exposure levels are unknown or where air-purifying respirators may not provide adequate protection.

Hand protection: Chemical resistant gloves. Consider double gloving.

Eye protection: Wear safety glasses with side shields (or goggles). If the work environment or activity involves dusty conditions, mists or aerosols, wear the appropriate goggles. Wear a faceshield or other full face protection if there is a potential for direct contact to the face with dusts, mists, or aerosols.

Skin and Body Protection:	Additional body garments should be used based upon the task being performed (e.g., sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces. Use appropriate degowning techniques to remove potentially contaminated clothing.
Hygiene measures:	Wash skin thoroughly with soap and water.

9 PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance:	
Physical State:	Solid
Form:	Powder
Color:	White, Gray
Solubility(ies):	
Solubility in Water:	Soluble

10 STABILITY AND REACTIVITY

Stability:	Stable
Possibility of hazardous reactions:	Stable
Conditions to avoid:	Excessive heat. Moisture.
Incompatible materials:	No data available.
Hazardous decomposition products:	Thermal decomposition or combustion may liberate carbon oxides and other toxic gases or vapors.

11 TOXICOLOGICAL INFORMATION

General information:	The information presented below pertains to the individual ingredients, and not to the mixture(s) or final formulations.

Specified substance(s):

Acute Toxicity (Oral);

Name	Test results
Propylene Glycol	LD50 (Rat): > 20 g/kg
Emamectin benzoate	LD50 (Rat): 76 - 88 mg/kg Toxic if swallowed. (Mouse): 21 - 31 mg/kg Toxic if swallowed.

Acute Toxicity (Dermal):

Name	Test results
Propylene Glycol	LD50 (Rat): > 20 g/kg
Emamectin benzoate	LOEL - Lowest Observable Effect Level (Rabbit): 500 mg/kg Harmful in contact with skin.

Acute Toxicity (Inhalation):

Name	Test results
Propylene Glycol	LC50 (Rat, 8 h): 4.1 mg/l No mortality observed.
Emamectin benzoate	LC50 (Rat, 4 h): > 1.049 mg/l Harmful if inhaled.

Repeated dose toxicity:

Name	Test results
Propylene Glycol	In rare cases, repeated excessive exposure may cause: central nervous system effects.
Emamectin benzoate	NOAEL (Rat, Oral, 14 Weeks, daily): 0.5 - 1.0 mg/kg NOEL (Rat, Oral, 14 Weeks, daily): (Target Organ(s): central nervous system, Peripheral nervous system) In repeat-dose toxicity studies in rats serious or significant adverse effects were observed in the following organs: nervous system , May cause nervous system damage. Data referenced is based on the benzoate salt. Data referenced is based on the hydrochloride salt. NOAEL (Rat, Oral, 53 Weeks, daily): 1.0 mg/kg NOEL (Rat, Oral, 53 Weeks, daily): (Target Organ(s): central nervous system, Peripheral nervous system) In repeat-dose toxicity studies in rats serious or significant adverse effects were observed in the following organs: nervous system , May cause nervous system damage. Data referenced is based on the benzoate salt. Data referenced is based on the hydrochloride salt. NOAEL (Dog, Oral, 14 Weeks, daily): 0.25 mg/kg NOEL (Dog, Oral, 14 Weeks, daily): (Target Organ(s): central nervous system, Peripheral nervous system, skeletal muscle) May cause nervous system damage. May cause muscle damage. Data referenced is based on the benzoate salt. Data referenced is based on the hydrochloride salt. NOAEL (Mouse, Oral, 79 Weeks, daily): 2.5 mg/kg NOEL (Mouse, Oral, 79 Weeks, daily): (Target Organ(s): central nervous system, Peripheral nervous system) May cause nervous system damage. Data referenced is based on the benzoate salt. Data referenced is based on the hydrochloride salt. NOAEL (Rat, Oral, 105 Weeks, daily): 0.25 mg/kg NOEL (Rat, Oral, 105 Weeks, daily): (Target Organ(s): central nervous system, Peripheral nervous system, liver, bladder) May cause nervous system damage. May cause liver damage. May cause bladder damage. Data referenced is based on the benzoate salt. Data referenced is based on the hydrochloride salt.

Inhalation: Harmful if inhaled.

Ingestion: Toxic if swallowed.

Skin corrosion/irritation: No data available.

Serious eye damage/eye irritation: No data available.

Respiratory sensitizer/Skin sensitizer:	No data available for finished product. Active veterinary ingredient: Not a skin sensitizer.
Carcinogenicity:	No data available for finished product. Active veterinary ingredient: No evidence of carcinogenicity in rats and mice. Not listed as carcinogen by OSHA, NTP or IARC.
Mutagenesis:	No data available for finished product.
Reproductive toxicity:	No data available for finished product. Active veterinary ingredient: Adverse developmental and reproduction effects were observed in rats. Adverse neonatal and fetal effects were observed in rats. Fetotoxicity was observed in rats. Tremors, hindlimb extension, reduced body weight gain were observed in rat pups; neuronal degeneration of brain or spinal cord in F0 rats. No teratogenicity observed in rats or rabbits at low doses. In rats at the highest dose group (8 mg/kg/day), there was increased number of fetuses with supernumerary ribs and an increased incidence of delayed ossification.
Other Effects:	No additional information

12 ECOLOGICAL INFORMATION

General information:	The information presented below pertains to the individual ingredients, and not to the mixture(s) or final formulations.
Ecotoxicity:	
Product:	
Chronic Toxicity(Fish):	No data available.

Specified substance(s):

Acute toxicity(Fish):

Name	Test results
Propylene Glycol	LC50 (Rainbow Trout (Oncorhynchus mykiss), 96 h): 44 - 51.6 g/l
Emamectin benzoate	LC50 (Rainbow Trout (Oncorhynchus mykiss), 96 h): 0.174 mg/l LC50 (Bluegill (Lepomis macrochirus), 96 h): 0.180 mg/l LC50 (Sheepshead minnow (Cyprinodon variegatus), 96 h): 1.34 mg/l

Acute toxicity(Aquatic invertebrates):

Name	Test results
Propylene Glycol	EC 50 (Water flea (Daphnia magna), 48 h): 4.85 - 34 g/l
Emamectin benzoate	EC 50 (Water flea (Daphnia magna), 48 h): 0.00099 mg/l EC 50 (Mysid (Americamysis bahia), 48 h): 0.000043 mg/l

Chronic Toxicity(Aquatic invertebrates):

Name	Test results
Propylene Glycol	No data available.
Emamectin benzoate	Maximum acceptable toxicant concentration (MATC) (Water flea (Daphnia magna)): 0.12 ug/l

Acute toxicity(Aquatic plants):

Name	Test results
Propylene Glycol	EC 50 (Green algae (Pseudokirchneriella subcapitata)): 19 g/l (growth inhibition)
Emamectin benzoate	No data available.

Persistence and degradability: No data available for finished product. Active veterinary ingredient: Expected to biodegrade.

Bioaccumulative potential: No data available for finished product. Active veterinary ingredient: Not expected to bioaccumulate.

Mobility: No data available for finished product. Active veterinary ingredient: Expected to be immobile in soil.

13 DISPOSAL CONSIDERATIONS

Disposal Methods: Disposal must be in accordance with applicable national, state/provincial, and/or local regulations.

Measures for Avoidance and Recovery: Incineration is the most effective method of disposal in most instances. Do not allow runoff to sewer, waterway or ground. Operations that involve the crushing or shredding of waste materials or returned goods should take into account recommended exposure limits where they exist.

14 TRANSPORT INFORMATION

DOT

Not regulated.

IMDG - International Maritime Dangerous Goods Code

UN number	UN3077
Proper Shipping Name	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S.(Emamectin benzoate)
Class	9
Packing group	III
Label(s)	9
Subsidiary risk label	
Marine Pollutant /	Envir. Hazardous, Labels Only
EmS No.	F-A; S-F

IATA - International Air Transport Association

UN number	UN3077
Proper Shipping Name	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S.(Emamectin benzoate)
Class	9
Packing group	III
Label(s)	9MI
Subsidiary risk label	

15 REGULATORY INFORMATION

US Regulations

- **CERCLA Hazardous Substance List (40 CFR 302.4):**
  None

- **Clean Water Act Section 311 Hazardous Substances (40 CFR 117.3):**
  None

- **Clean Air Act (CAA) Section 112(r) Accidental Release Prevention (40 CFR 68.130):**
  None

SARA Title III

- **Section 302 Extremely Hazardous Substance (40 CFR 355, Appendix A):**
  None

- **Section 313 Toxic Release Inventory (40 CFR 372):**
  None present or none present in regulated quantities.

State Regulations

- **California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65):**

Butylated hydroxyanisole	Hazard Designation: Carcinogenic.

- **Massachusetts Right-To-Know List:**

Starch	Listed
Butylated hydroxyanisole	Listed

- **New Jersey Right-To-Know List:**

Propylene Glycol	Listed

- **Pennsylvania Right-To-Know List:**

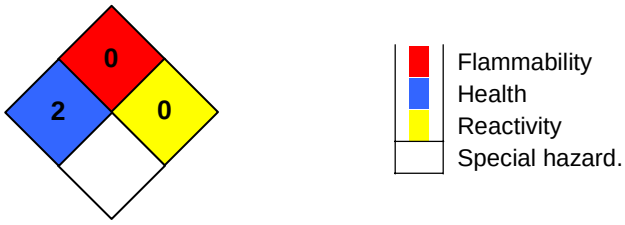
Starch	Listed
Propylene Glycol	Listed

16 OTHER INFORMATION

OTHER INFORMATION

This SDS is written to provide health and safety information for individuals who will be handling the final product formulation during research, manufacturing, and distribution. For health and safety information for individual ingredients used during manufacturing, refer to the appropriate SDS for each ingredient. Refer to the package insert or product label for handling guidance for the consumer.

NFPA Hazard ID



Hazard rating: 0 - Minimal; 1 - Slight; 2 - Moderate; 3 - Serious; 4 - Severe

Revision Information: Not relevant.
Issue Date: 06.12.2013
Disclaimer: This information is provided without warranty. The information is believed to be correct. This information should be used to make an independent determination of the methods to safeguard workers and the environment.

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® (emamectin benzoate) medicated feed. The Investigator is responsible for accurate completion of Form SLICE-W.
2. Investigator should keep the original on file, and fax a copy to the Study Monitor for review.
3. After review, the Study Monitor will fax a copy to the AADAP Office for assignment of the Study Number.
4. The AADAP Office will review the worksheet, and then fax the assigned trial Study Number to both the Investigator and Study Monitor, at which time the trial may be initiated.
5. **Note**: Both Investigator and Study Monitor should sign and date Form SLICE-W.

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: Describe in detail the purpose of the clinical trial. Study design must be carefully focused and lend itself to rigorous evaluation. If more space is required to describe study details, title additional page(s) "Study Design" and attach them to this Worksheet.

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 Material 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® (emamectin benzoate) premix or SLICE® (emamectin benzoate) medicated feed.
2. Investigator should keep the original on file, and send one copy to the Study Monitor for review.
3. Within 10 days of receipt, the Study Monitor should send a copy to the AADAP Office.
4. **Note:** Both Investigator and Study Monitor should sign and date Form SLICE-1.

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.

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	*To be Determined*		
Source of Drug	Western Chemical Inc.		
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 (yes/no)	-----
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: _____ **Sponsor:** _____

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

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 regimes.
3. A signed copy of Form 2a should be sent to the Study Monitor at the end of the Study Year.
4. Original Form 2a should be archived at the investigating facility.

Qty on Hand from
previous page (ml) _____ Facility _____ Reporting individual_____

SLICE® Premix Lot Number	Date Received	Amount Received (g)	Date Used	Study Number	SLICE® Premix Used for Teatment (g)	SLICE® Premix Shipped[1] (g)	SLICE® Premix Disposal (g)	SLICE® Premix On-Hand (g)	Inventory by (initials)

[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: _____ **Study Monitor:** _____

Signature and Date Signature and Date

Form SLICE-2a. 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 regime.
3. A signed copy of Form 2b should be sent to the Study Monitor at the end of the study, or at the end of the Study Year.
4. Original Form 2b should be archived at the investigating facility.

Qty on Hand from
previous page (ml) _____ Facility _____ Reporting individual_____

SLICE® Medicataed Lot Number	Date Received	Amount Received (g)	Date Used	Study Number	SLICE® Medicataed Used for Teatment (g)	SLICE® Medicataed Shipped[1] (g)	SLICE® Medicataed Disposal (g)	SLICE® Medicataed On-Hand (g)	Inventory by (initials)

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

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

Investigator: _____ **Study Monitor:** _____

Signature and Date Signature and Date

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

INSTRUCTIONS

1. Investigator must fill out Form SLICE-3 no later than 10 days after completion of treatment. Study Number must be recorded on all pages of Form SLICE-3. Attach lab reports and other information.
2. If SLICE® (emamectin benzoate) was not used under the assigned Study Number, fill out only the Site Information portion on this page, and skip to the end of page 4 and fill out only the "Negative Report" section.
3. Investigator should keep the original on file, and send a copy to the Study Monitor. Within 10 days of receipt, the Study Monitor should send a copy to the AADAP Office for inclusion in the permanent file.
4. **Note**: Both Investigator and Study Monitor should sign and date Form SLICE-3.

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 vs dry, particle size)			
Feed rate (% BW fed per day)			
Date treatment initiated		Date treatment completed	

Daily Mortality Record

INSTRUCTIONS

1. Investigator must 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. Use additional copies of this form if more than 6 rearing units are involved in the trial.

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	**5**									
	4									
	3									
	2									
	1									
Treatment	**1**									
	2									
	3									
	4									
	5									
	6									
	7									
Post-Treatment Period	**1**									
	2									
	3									
	4									
	5									
	6									
	7									
	8									
	9									
	10									

Daily Mortality Record (Supplemental Post-treatment Period Data)

INSTRUCTIONS

1. Investigator should fill out the Daily Mortality Record (Supplemental Post-treatment Period Data) only if data is collected for more than 10 days post-treatment.
2. Use additional copies of this form if more than 6 rearing units are involved in the trial.

FACILITY										
	Rearing Unit ID									
	Treated or Control									
	Number of Shrimp									
	Day	Date	Water Temp (F°)	Mortality	Mortality	Mortality	Mortality	Mortality	Mortality	Daily Observer Initials
Post - Treatment Period	11									
	12									
	13									
	14									
	15									
	16									
	17									
	18									
	19									
	20									
	21									
	22									
	23									
	24									
	25									
	26									
	27									
	28									

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 OF TREATED FISH:

Observed withdrawal period:

_____ Investigator should initial here to indicate compliance with established withdrawal period

_____ 60 days

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 (Investigator should initial for negative reports as soon as the Study Number is known to be no longer needed or valid

Date Prepared: _____ **Investigator:** _____

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

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	

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	

[1] Additional copies of table for post-treatment infestation level are available on page 2 of this form

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

☐ Additional Documentation of Level of Parasite Infestation Post-Treatment

Note: If data on post-treatment level of parasite infestation is only collected once, please simply write "N/A" in the box

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	
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		26	
		27	
		28	
		29	
		30	

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