STUDY PROTOCOL FOR AN AQUACULTURE INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR AQUAFLOR® (florfenicol) USE AS A FEED ADDITIVE (INAD #10-697)

Sponsor:

U.S. Fish and Wildlife Service, Office of Fisheries

_____ _____
Sponsor Signature Date Approved

Manufacturer:

Intervet/Schering-Plough Animal Health
1095 Morris Avenue
Union, NJ 07083-1982

Facility for Coordination of Aquaflor® as a Feed Additive INAD:

Aquatic Animal Drug Approval Partnership Program
U.S. Fish and Wildlife Service
4050 Bridger Canyon Road
Bozeman, Mt 59715

Proposed Starting Date: February 1, 2009

Proposed Ending Date: January 31, 2012

Study Director: Mr. Jim Bowker (USFWS/AADAP)

_____ _____
Study Director Signature Date

Clinical Field Trial Location and Trial Number:

_____ _____
Facility Name

Investigators Name

_____ _____
Investigator Signature Date

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STUDY PROTOCOL FOR A SUPPLEMENTAL AQUACULTURE INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR AQUAFLOR® USE AS A FEED ADDITIVE UNDER INAD #10-697

I. STUDY ID AND TITLE

Clinical field trials to determine the efficacy of feeding Aquaflor® to cultured fish to control certain bacterial diseases. INAD #10-697. **[Note: No clinical field trials will be conducted under this INAD for use patterns for which Aquaflor® has already received FDA-approval (e.g., treatment of ESC in catfish, treatment of coldwater disease or furunculosis in freshwater-reared salmonids (NADA 141-246), and treatment of columnaris in catfish (NADA 141-259)].**

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
1095 Morris Avenue
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Contact person: Dr. Richard Endris, Research Program Manager
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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

Study Monitors for Aquaflor® INAD: 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: February 1, 2009

Proposed Completion Date: January 31, 2012

V. BACKGROUND/PURPOSE

Florfenicol is a potent, broad spectrum antibacterial agent with bacteriostatic properties (Horsberg et al 1996). It is a fluorinated analogue of thiamphenicol, and is similar in structure to chloramphenicol. Both thiamphenicol and chloramphenicol have been used as broad spectrum veterinary antibiotics (Nagata and Oka 1996). Aquaflor® is an aquaculture premix containing the novel antibiotic, florfenicol. Aquaflor® is available only from Schering-Plough Animal Health. For additional information on florfenicol and Aquaflor® see Addendum II.

Bacterial diseases remain a major problem in aquaculture and account for significant losses of fish (Bjorndal 1990; Clarke and Scott 1989; Frefichs and Roberts 1989). While the importance of environmental conditions (Hastien 1988; McCarthy and Roberts 1980; Munro and Roberts 1989) and the value of effective vaccines, where available (Ellis 1989), are acknowledged, antimicrobial therapy presently has an important role to play in aquaculture (Alderman 1988; Klontz 1987).

The efficacy of florfenicol against furunculosis in Atlantic salmon, *Salmo salar*, has been demonstrated in several studies (Samuelsen et al., 1998; Nordmo et al., 1994). Efficacy has also been demonstrated against other fish diseases, such as pseudotuberculosis in yellowtail (buri), *Seriola quinqueradiate*, (Yasunaga and Yasumoto 1988) and vibriosis in goldfish, *Carassius auratus,* and infections by *Edwardsiella tarda* in Japanese eel *Anguilla japnica* (Fukui et al. 1987). Aquaflor® is currently approved in Canada for the control of furunculosis in Atlantic salmon.

Florfenicol has great potential for treatment of infectious diseases, and because of existing data on human food safety and high potency, it could become a major drug in veterinary medicine, with special value in animal foods (Powers et al. 1990). Thus, Aquaflor® has become a strong candidate for use in aquaculture, and there is considerable interest by the aquaculture community in the U.S. to pursue approval of this drug for use in fish culture by FDA.

The objective of these field based clinical efficacy trials is to evaluate the efficacy of Aquaflor® medicated feed treatment to control mortality in a variety of fish species caused by pathogens susceptible to florfenicol. Efficacy trials will be conducted at a number of different study sites, on a variety of fish species infected with a variety of fish pathogens. Diseases of interest include, but are not limited to: 1) systemic columnaris; 2) furunculosis,3) enteric redmouth; and 4) bacterial hemorrhagic septicemia caused by Aeromonads and Pseudomonads.

VI. SPECIFIC OBJECTIVES

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

1. Collect scientific data necessary to support pivotal efficacy trials to further establish the effectiveness of Aquaflor® as a feed additive to control certain bacterial diseases of fish that occur in a variety of environmental conditions, at a wide range of temperatures, and in a variety of cultured fish species. **[Note: No clinical field trials will be conducted under this INAD for use patterns for which Aquaflor® has already received FDA-approval (e.g., treatment of ESC in catfish and treatment of coldwater disease or furunculosis in freshwater-reared salmonids (NADA 141-246), and treatment of columnaris in catfish (NADA 141-259)].**

2. Provide an opportunity for fish culturists to legally use Aquaflor® as a feed additive

to control certain bacterial diseases of fish that occur in a variety of environmental conditions, at a wide range of temperatures, and in a variety of cultured fish species so that they can maintain healthy stocks of fish during the period of time necessary for collection of data that will be used to support an expanded NADA(s) for the use of Aquaflor® in various fish species.

Specific study objectives are described below:

Objective A

Determine if the Aquaflor® use pattern for which the drug has already been labeled in the U.S. for the control of specific bacterial pathogens in specific fish species (i.e., **10 mg of florfenicol per kg of fish per day for 10 consecutive days**) is efficacious when fed as a feed additive for the control of mortality caused by 1) these same bacterial pathogens in additional species, and 2) other bacterial pathogens (including enteric redmouth, bacterial hemorrhagic septicemia caused by Aeromonads and Pseudomonads, and other gram negative systemic bacteria) in a broad variety of fish species when cultured under a variety of rearing or environmental conditions. Salmonid fish species treated in this manner may be released for immediate harvest after a 21-day withdrawal period (from the date of last treatment). Non-salmonid fish species treated in this manner may be released for immediate harvest after a 28-day withdrawal period. No withdrawal period will be required for fish that will not be catchable during the above-described withdrawal periods, or are illegal for harvest during those periods.

Objective B

Determine if Aquaflor® treatment at a dosage of **15 mg of florfenicol per kg of fish per day for 10 consecutive days** is efficacious (or in some cases possibly more efficacious than treatment at a dosage of 10 mg of active drug per kg of fish per day for 10 consecutive days) when fed as a feed additive to control morality caused by a variety of bacterial pathogens in a variety of fish species cultured under a variety of environmental conditions. Salmonid fish species treated in this manner may be released for immediate harvest after a 21-day withdrawal period (from the date of last treatment). Non-salmonid fish species treated in this manner may be released for immediate harvest after a 28-day withdrawal period. No withdrawal period will be required for fish that will not be catchable during the above-described withdrawal periods, or are illegal for harvest during those periods.

VII. MATERIALS

A. Test and Control Articles:

1. Drug Identity

a. Active ingredient

Schering-Plough Animal Health's feed additive Aquaflor® containing 500 grams of florfenicol per kg of premix will be the only form of the drug used by fish food manufacturers to formulate treated feed, or by Investigators to top-dress feed.

b. Chemical name - active component(s)

D-(threo)-1-(p-methylsulfonylphenyl)-2-dichloroacetamide-3-fluoro-1-propanol. This is the final formula. Florfenicol is a pure compound with no inactive ingredients.

c. Molecular formula

$C_{12}H_{14}NO_4C_{12}FS$

d. Molecular weight

358.20

e. Appearance and odor

White amorphous lumpy powder

f. Strength and dosage form

Drug concentration in the diet and feeding regimes will be designed to provide a daily dosage of either 10 or 15 mg of active drug per kg of fish.

g. Manufacturer, source of supply

Intervet/Schering-Plough Animal Health
1095 Morris Avenue
Union, NJ 07083-1982

Contact person: Dr. Richard Endris, Research Program Manager
Telephone: (908) 473-3133
Fax: (908) 473-3654

h. Additional information

See Addendum II.

2. Verification of Drug Integrity/Strength

Schering-Plough Animal Health will provide limited analytical support in the event questions arise regarding product quality and drug activity. Presently, no provisions are in place to assay medicated feed used in supplemental efficacy trials. However, medicated feed used in pivotal efficacy trials will be assayed to verify drug integrity/strength. Investigators must record treated feed lot number, or chemical lot number of premix if top-coating, on Form FFC-1 Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals.

Based on discussions with Investigators concerning planned feed rate and kg of fish to be medicated, commercial fish feed manufacturers shall prepare feed with concentrations of Aquaflor® premix to assure that target dosages of either 10 or 15 mg florfenicol/kg fish/day

are achieved.

The Investigator may also prepare his/her own drug-treated feed by top-dressing feed on-hand (or specially ordered feed) with Aquaflor® premix. If the Investigator chooses this option, they are encouraged (but not required) to have a sample of the top-dressed feed assayed for florfenicol concentration by a certified, analytical testing laboratory. Results of drug-treated feed assays should be reported on Form FFC-3.

3. Storage Conditions

Treated feed will be stored at temperatures and for periods of time not to exceed limits set by the feed manufacturer. Treated feed should be ordered only as needed and not stored for possible future use.

Premix should be stored at temperatures and for periods of time not to exceed the limits set by Intervet/Schering-Plough Animal Health. Inventories of both treated feed and premix on-hand must be recorded on either Form FFC-2a or Form FFC-2b, Chemical Use Log for Aquaflor®.

4. Handling Procedures

Each Study Monitor and Investigator will be required to have a current copy of the Material Safety Data Sheet (MSDS) for Aquaflor® (Appendix IV). Each person involved with the study and each person who may be present during the use of Aquaflor® shall be required to read the MSDS. Safety precautions as outlined in the MSDS will be followed at all times when working with Aquaflor®. Standard laboratory equipment such as gloves, lab coats or aprons, eye protection, etc., should be worn at all times.

The possible hazards associated with the handling of Aquaflor® treated feed should be discussed, at least once per year, at station Safety meetings. Individuals with known allergic reactions to florfenicol (i.e. Aquaflor®) will not be permitted to handle such feed. For transportation emergencies telephone CHEMTREC, 800/424-9300.

5. Investigational labeling

Copies of the labels to be attached to each bag of Aquaflor® treated feed are provided in Appendix V. It is the responsibility of the Investigator to ensure proper labeling of all bags of treated feed.

6. Accountability

1. USFWS Facilities and Non-USFWS Facilities

Immediately upon receiving an order/shipment of Aquaflor® treated feed or Aquaflor® premix, the Investigator must complete Form FFC-1 “Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals”. The Investigator will archive the original in the facility’s INAD file, and send a copy to his/her Study Monitor. Both the Investigator and the Study Monitor are required to sign Form FFC-1. The Study Monitor will then forward a copy to the Study Director at the AADAP Office. The Study Director will archive one copy,

and send two copies of Form FFC-1 to FDA. Arrangements should be made between Investigators and Study Monitors to insure completed Form FFC-1s are received by the Study Director in a timely manner.

Investigators are also responsible for maintaining an accurate inventory of Aquaflor® treated feed and/or Aquaflor® premix on hand. Chemical Use Logs (Form FFC-2a and Form FFC-2b) will be supplied to each Investigator. Each time Aquaflor® treated feed and/or Aquaflor® premix is used, it must be reported by the Investigator on either Form FFC-2a or Form FFC-2b, respectively.

B. Items Needed for Sample Collection, Observations, Etc.:

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

VIII. EXPERIMENTAL UNIT

The experimental unit in these clinical field trials will consist of contained or isolated groups of fish. This could be groups of fish contained in tanks, raceways, or ponds.

IX. ENTRANCE CRITERIA

Bacterial fish pathogens should be presumptively identified by procedures described in Section 1, Chapter 1 of the American Fisheries Society/Fish Health Section Blue Book "Suggested Procedures for the Detection and Identification of Certain Finfish and ShellfishPathogens, 2005 Edition. Other, more sensitive methods described elsewhere in peer-reviewed references, or as mutually determined by the local fish health biologist, in consultation with the Study Monitor, also may be used. (**Note**: **Diagnostic methods other than those in the 2005 Edition of the "Blue Book" should be described on a separate sheet attached to Form 3 "Diagnosis and Treatment Record"**).

Other entrance criteria for the use of Aquaflor® as a feed additive are as follows:

1. The proposed facility and the investigator must be listed in Appendix IIIa of this Study Protocol before drug-treated feed can be ordered and dispensed under this INAD. Last minute deviations can be requested by the Sponsor, the Study Director, or by an Investigator to control emergency disease outbreaks (See Section XX).

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

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

bacterial agent must be identified.

4. Since the efficacy of Aquaflor® therapy for the control of a specific disease 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 Aquaflor® therapy. Complicating bacterial or parasitic diseases should be carefully documented. If necessary, these infections can be treated once Aquaflor® response (efficacy) data has been collected. However, it may take as long as several weeks after the completion of Aquaflor® therapy to determine differences between test and control groups and to complete post-treatment bacteriological evaluations.

Prior to initiating each treatment event, the Investigator must first complete a Form FFC-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 worksheet 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. The Investigator should record the assigned study number on Form FFC-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 is rapidly escalating, the Investigator should contact the AADAP Office for a study number and permission to proceed.

X. TREATMENT GROUPS

Separately confined, untreated control fish will not be required in all supplementary studies conducted to determine the effectiveness of Aquaflor® treatment. Fish from a group or lot will first be examined to determine if treatment with Aquaflor® 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 some cases degree or severity of bacterial infestation will also be quantitated.

Although untreated control groups are not a required element of treatment under this INAD exemption and are at the discretion of the Investigator, use of separately confined untreated control groups are strongly encouraged whenever circumstances permit. Control groups are extremely important to not only document disease virulence and disease 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. Although not required, replicate treatment groups are strongly encouraged in both treated and control groups.
Blinded studies can reduce bias in data collection. Whenever possible, investigators should consider methods by which mortalities are tallied and morbidity observations recorded by individuals who are unaware which test units have been treated and which test units are serving as controls.

The designation of specific treatment groups often depends upon the number of affected treatment units, the nature and severity of the disease being treated, and the variables being

tested. Two or three different treatment groups are generally anticipated.

1. **Spotty, low level, or chronic disease patterns:**

   A number of facilities participating in this INAD are doing so as a means of being prepared, in advance, to use Aquaflor® treated feed in the event a bacterial disease outbreak occurs. If management practices have been good, disease occurrences often result in low morbidity and mortality rates. Aquaflor® therapy may be occasionally required as a part of the process of a comprehensive fish health management program. These situations are the most typical. Even though there may be too few units involved to allow for treatment replication, careful record keeping is important so that useful data can be collected. Handling of clinically ill fish should be kept to a minimum until they have been successfully treated. Even the careful separation of diseased fish into new groups for treatment may alter environmental conditions present during disease initiation, thereby potentially rendering the Aquaflor® therapy trial meaningless.

2. **Epizootics:**

   At some participating facilities disease outbreaks may be more widespread, more severe, and occur more regularly. Sufficient fish and test units at these facilities may be available to conduct higher quality studies (i.e. replication, randomization, blinding, etc.). Such situations are suitable for the conduct of pivotal, carefully designed and controlled studies following the Aquaflor® pivotal study protocol FLOR-99-EFF (available from the AADAP Office). Fish should be treated in place whenever possible without changing the circumstances bringing on the disease. These facilities will be given top priority for the availability of treated feed, assistance from monitors and AADAP personnel, and diagnostic support from fish health biologists.

XI. Treatment Schedules

A. Dosage and duration:

Objective A: For the control of mortality caused by a variety of bacterial pathogens, in a variety of fish species, and under a variety of environmental conditions. Aquaflor® will be fed at the rate of **10 mg of florfenicol per kg of fish per day for 10 consecutive days**.

Objective B: For the control of mortality caused by a variety of bacterial pathogens, in a variety of fish species, and under a variety of environmental conditions. Aquaflor® will be fed at the rate of **15 mg of florfenicol per kg of fish per day for 10 consecutive days**.

B. Fish species:

Fish stocks listed in Appendix VIa may be fed Aquaflor® treated feed in clinical field trials.

C. 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 some cases, feeding fish only treated feed may work best. In other cases, feeding fish treated feed first (i.e., early in the day) followed by the feeding of 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. However, in all cases, the daily feeding regime should be designed to maximize consumption of the treated feed to result in consumption of the intended dosage of either 10 or 15 mg florfenicol 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.

XII. TREATMENT RESPONSE PARAMETERS

The collection and reporting of source data begins with the detection of a disease warranting Aquaflor® treatment. Case history records, daily morbidity and mortality records, as well as any extenuating or mitigating circumstances that may affect treatment response need to be documented. Treatment response parameters that should be addressed include the following:

1. Primary Parameters

Morbidity and mortality data, coupled with case history and bacteriological analyses, usually indicate when Aquaflor® treatment is needed. **This source data must be collected for at least 10 days before treatment, during treatment, and for up to at least 21 days after the treatment period has ended**. Collection of this data is critically important in all cases. Samples of kidney or other tissue will be removed from groups of representative fish and tested by bacteriological, serological, or other methods to determine the presence of target pathogens.

2. Secondary Parameters

Secondary parameters include observations on the acceptability of treated feed, growth data from treated vs untreated fish, or other observations fish culturists believe relate directly to Aquaflor® therapy. Specify on source data sheets how fish were fed (e.g. by hand, using automatic feeders, utilizing demand feeders) and whether feed was well accepted or poorly utilized

3. Adverse Reactions

All treated fish should be closely observed for signs of aversion (rejection) to treated feed or clinical signs of drug toxicity. Any adverse reactions to treatments should be documented on source data sheets and reported immediately 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 analyses can be performed. The importance of investigator observations/comments cannot be overemphasized.

XIII. FORMS FOR DATA COLLECTION

When the Study Protocol has been approved and treatments are scheduled, the Investigator at each facility covered by the Aquaflor® INAD 10-697 will need to complete the following forms:

Form FFC-W. Worksheet for Designing Individual Field Trials under INAD #10-697

Form FFC-1. Report on Receipt of Drug - Guide for reporting investigational new animal drug shipments for poikilothermic food animals.

Form FFC-2a. Chemical use log for clinical field trials using Aquaflor® as a feed additive under INAD #10-697 - Aquaflor® Premix.

Form FFC-2b. Chemical use log for clinical field trials using Aquaflor® as a feed additive under INAD #10-697 - Aquaflor® Medicated Feed.

Form FFC-3. Diagnosis, treatment, and mortality record for clinical field trials using Aquaflor® as a feed additive under INAD #10-697.

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. Salmonid fish species will be maintained at culture facilities for a specified 21-day withdrawal period (from the date of last treatment). Non-salmonid fish species will be maintained at culture facilities for a specified 28-day withdrawal period.

No withdrawal period will be required for fish that will not be catchable during the above-described withdrawal periods, or are illegal for harvest during those periods. No withdrawal period shall be required for dead fish that will be buried or rendered into non-edible products.

The Investigator must record the disposition of all treated fish on Form 3.

XVI. DISPOSITION OF INVESTIGATIONAL DRUG

Aquaflor® treated feed will be used only in the manner and by the individuals specified in the Study Protocol. Any Aquaflor® treated feed remaining at the end of a study should be disposed of in a landfill or by burial. If by chance there is a bona fide need for unused drug-treated feed immediately following completion of a treatment regimen, Investigators should consult with Study Monitors to determine if unused feed is appropriate for further use. Supplemental use of unused drug-treated feed is allowed only with Study Monitor approval. The investigational drug may not be redistributed to others not specified by the protocol and may not be retained by the Investigator after completion of the study.

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

A. Drug distribution

Intervet/Schering-Plough Animal Health's feed additive Aquaflor® containing 500 grams of florfenicol per kg of premix will be the only form of the drug used by fish food manufacturers to formulate treated feed, or by Investigators to top-dress feed. Intervet/Schering-Plough Animal Health will provide Aquaflor® for use in clinical field trials to the AADAP Office for "warehousing." The AADAP Office will in turn provide Aquaflor® to Investigators (or feed manufacturers) only upon receipt and approval of a completed Form FFC-W.

See Section VII.A.6. Accountability (page 5) for additional information and details.

B. Study Monitors

The Study Monitors are generally fish health professionals with experience in diagnosing and treating fish diseases. There is one Study Monitor assigned to each facility within the USFWS that is covered by the Aquaflor® INAD 10-697. Non-service facilities must have a similar Study Monitor - Investigator relationship in place. A list of Study Monitors, along with addresses and phone numbers, can be found in Appendix II. The Study Monitors are responsible for supervision of the trials, adherence of Investigators to the Study Protocol, and inspection of the sites.

C. Special equipment and materials

Most of the equipment and materials required for this study (with the exception of the Aquaflor® itself) are already available at each fish hatchery. Diagnosis and treatment of diseases of fish 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

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

E. Drug accountability records

See Section VII.A.6. Accountability (page 5) for details and Form FFC-W, Form FFC-1, Form FFC-2a, Form FFC-2b, and Form FFC-3 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 Monitor who will ensure that all required information is provided. The Study Monitor 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. **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. The Investigator is also responsible for archiving a complete set of all original data. Upon receipt of drug, a copy of Form FFC-1 should be sent immediately to the Study Monitor, who will in turn forward a copy to the Study Director. Copies of Forms FFC-2a and FFC-2b should be sent to the Study Monitor at the end of the calendar year, or with a corresponding Form FFC-3. Copies of Form FFC-3 should be sent to the Study Monitor within 10 days of completion of a study. The Study Monitor will carefully check each set of data for accuracy and completeness. If there are any discrepancies in the data, the Study Monitor will contact the Investigator immediately to rectify the problem. After review, Study Monitors will forward all data to the Study Director. As stated above, the complete set of raw data will 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.

Form FFC-3 Report on Efficacy of Treatments is to be completed no later than 10 days after a course of therapy is completed. The purpose of this form and supplementary data is to document the results of the treatment. In addition to the data solicited by the form,

attach original source data on daily mortalities occurring in all rearing units involved in the clinical field trial during the 10-day period prior to treatment, during treatment, and during the 21-day period following the completion of drug therapy.

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. An annual report will be prepared by the AADAP Office and submitted to the FDA. 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 FDA.

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). 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 differently 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 contacted immediately for advice. **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 the quarterly data summaries, and ultimately be submitted to the Study Director.

Merck Animal Health
One Merck Dr.
Whitehouse Station, NJ 08889

MATERIAL SAFETY DATA SHEET

Merck Animal Health urges each user or recipient of this MSDS to read the entire data sheet to become aware of the hazards associated with this material.

SECTION 1. IDENTIFICATION OF SUBSTANCE AND CONTACT INFORMATION

MSDS NAME: **Florfenicol Powders**

SYNONYM(S): Florfenicol Powders
AQUACOL VET Medicated Premix for Salmon
AQUAFLOR 50% Medicated Premix for Salmon
AQUAFLOR Type A Medicated Article
FLOROCOL

MSDS NUMBER: SP000956

EMERGENCY NUMBER(S): (908) 423-6000 (24/7/365) English Only

Transportation Emergencies - CHEMTREC:
(800) 424-9300 (Inside Continental USA)
(703) 527-3887 (Outside Continental USA)

Rocky Mountain Poison Center (For Human Exposure):
(303) 595-4869

Animal Health Technical Services:
For Animal Adverse Events: Small Animals and Horses: (800) 224-5318
For Animal Adverse Events: Livestock: (800) 211-3573
For Animal Adverse Events: Poultry: (800) 219-9286

INFORMATION: Animal Health Technical Services:
For Small Animals and Horses: (800) 224-5318
For Livestock: (800) 211-3573
For Poultry: (800) 219-9286

MERCK MSDS HELPLINE: (800) 770-8878 (US and Canada)
(908) 473-3371 (Worldwide)
Monday to Friday, 9am to 5pm (US Eastern Time)

SECTION 2. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

Powder
White
Odor unknown
May cause allergic reactions in susceptible individuals.
May cause effects to:
gastrointestinal tract
male reproductive system
May cause impaired fertility.
May cause developmental effects.
Toxic to aquatic organisms.
May cause long-term adverse effects in the aquatic environment.

POTENTIAL HEALTH EFFECTS:

The toxicological properties of this material have not been characterized in humans. Therefore, laboratory or process control systems and appropriate work practices should be in place to minimize the potential for inhalation exposure, skin contact, eye contact, or ingestion when working with this material.

Only information about the ingredients that are expected to contribute significantly to the potential health hazard profile of the formulation(s) are presented.

This product is not for use in humans. Clinical effects in humans have not been determined.

Florfenicol, the active ingredient in this product, is a broad-spectrum antibiotic used in veterinary products. Florfenicol may cause allergic reactions in susceptible individuals. Based on animal studies, florfenicol may cause slight eye irritation, constipation, changes in blood cell counts, changes in stool, or liver effects. It may also cause developmental effects or effects to male reproductive organs.

Lactose is not expected to produce significant toxicity with workplace exposure. Lactose may cause irritation to the eyes, skin, and mucous membranes from mechanical action. Lactose may cause abdominal pain, bloating and diarrhea if ingested in large amounts or in lactose-intolerant individuals. Lactose may cause allergic reactions in sensitive individuals.

Povidone is not-irritating, not-sensitizing and practically not-toxic. Because povidone is not absorbed from the gastrointestinal tract, at high concentrations povidone can cause increased bowel activity, flatulence (gas), and severe constipation. These effects are not expected with occupational handling of the material.

LISTED CARCINOGENS

SECTION 3. COMPOSITION AND INFORMATION ON INGREDIENTS

PRODUCT USE: Aquaculture product

CHEMICAL FORMULA: Mixture.

The formulations for these products are proprietary information. These formulations have the same hazardous profile; however, the presence of hazardous ingredients may vary by formulation. Only hazardous ingredients in concentrations of 1% or greater and/or carcinogenic ingredients in concentrations of 0.1% or greater are listed in the Chemical Composition table. Active ingredients in any concentration are listed. For additional information about carcinogenic ingredients see Section 2.

CHEMICAL COMPOSITION

INGREDIENT	CAS NUMBER	PERCENT
Florfenicol	73231-34-2	50
Lactose	63-42-3	40-50
Povidone	9003-39-8	1-10

ADDITIONAL INFORMATION: This MSDS 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 MSDS for each ingredient. Refer to the package insert or product label for handling guidance for the consumer.

SECTION 4. FIRST AID MEASURES

INHALATION: Remove to fresh air. If any trouble breathing, get immediate medical attention. Administer artificial respiration if breathing has ceased. If irritation or symptoms occur or persist, consult a physician.

SKIN CONTACT: In case of skin contact, while wearing protective gloves, carefully remove any contaminated clothing, including shoes, and wash skin thoroughly with soap and water. If irritation or symptoms occur or persist, consult a physician.

EYE CONTACT: In case of eye contact, immediately rinse eyes thoroughly with plenty of water. If wearing contact lenses, remove only after initial rinse, and continue rinsing eyes for at least 15 minutes. If irritation occurs or persists, consult a physician.

INGESTION: Rinse mouth and drink a glass of water. Do not induce vomiting unless under the direction of a qualified medical professional or Poison Control Center. If symptoms persist, consult a physician.

NOTE TO PHYSICIAN: This product contains florfenicol, a broad spectrum antibiotic which may cause allergic reactions in susceptible individuals.

SECTION 5. FIRE FIGHTING MEASURES

FLAMMABILITY DATA:

Flash Point: Not determined (liquids) or not applicable (solids).

EXPLOSION HAZARDS:
Under normal conditions of use, this material does not present a significant fire or explosion hazard. However, like most organic compounds, this material may present a dust deflagration hazard if sufficient quantities are suspended in air. This hazard may exist where sufficient quantities of finely divided material are (or may become) suspended in air during typical process operations. An assessment of each operation should be conducted and suitable deflagration prevention and protection techniques employed.

The sensitivity of this material to ignition by electrostatic discharges has not been determined. In the absence of testing data, all conductive plant items and operations personnel handling this material should be suitably grounded.

SPECIAL FIRE FIGHTING PROCEDURES:
Wear full protective clothing and self-contained breathing apparatus (SCBA).

SUITABLE EXTINGUISHING MEDIA:
Carbon dioxide (CO_2), extinguishing powder or water spray.

See Section 9 for Physical and Chemical Properties.

SECTION 6. ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS:
Wear appropriate personal protective equipment as specified in Section 8. Keep personnel away from the clean-up area.

SPILL RESPONSE / CLEANUP:
All spills should be handled according to site requirements and based on precautions cited in the MSDS. In the case of liquids, use proper absorbent materials. For laboratories and small-scale operations, incidental spills within a hood or enclosure should be cleaned by using a HEPA filtered vacuum or wet cleaning methods as appropriate. For large dry or liquid spills or those spills outside enclosure or hood, appropriate emergency response personnel should be notified. In manufacturing and large-scale operations, HEPA vacuuming prior to wet mopping or cleaning is required.

ENVIRONMENTAL PRECAUTIONS:
This product is toxic to aquatic organisms. Do not allow product to reach ground water, water course, sewage or drainage systems.

See Sections 9 and 10 for additional physical, chemical, and hazard information.

SECTION 7. HANDLING AND STORAGE

HANDLING:
Keep containers adequately sealed during material transfer, transport, or when not in use. Wash face, hands, and any exposed skin after handling. Do not eat, drink, or smoke when using this substance or mixture.

Appropriate handling of this material is dependent on many factors, including physical form, duration and frequency of process or task, and effectiveness of engineering controls. Site-specific risk assessments should be conducted to determine the feasibility and the appropriateness of all exposure control measures. See Section 8 (Exposure Controls) for additional guidance.

STORAGE:
Store in a cool, dry, well ventilated area.

See Section 8 for exposure controls and additional safe handling information.

SECTION 8. EXPOSURE CONTROLS AND PERSONAL PROTECTION

The following guidance applies to the handling of the active ingredient(s) in this formulation.

OCCUPATIONAL EXPOSURE BAND (OEB):
OEB 2: 100-1000 mcg/m^3. Materials in an OEB 2 category are considered to be slight health hazards. The OEB is a range of airborne concentrations expressed as an 8-hour Time Weighted Average (8-hr. TWA) and is intended to be used with Industrial Hygiene Risk Assessment to assist with industrial hygiene sampling and selection of proper controls for worker protection. Consult your site safety and industrial hygiene staff for guidance on handling and control strategies.

OCCUPATIONAL EXPOSURE GUIDELINE (OEG):
An Occupational Exposure Guideline (OEG) of 80 mcg/m^3 (8-hr TWA) has been established for Florfenicol. Consult your site safety and industrial hygiene professional(s) for additional guidance.

HHC/OEG NOTATION(S):
This material has a notation of "A" for its ability to cause immediate allergic hypersensitivity reactions or anaphylaxis.

EXPOSURE CONTROLS
The health hazard risks of handling this material are dependent on many factors, including physical form, duration and frequency of process or task, and effectiveness of engineering controls. Site-specific risk assessments should be conducted to determine the feasibility and the appropriateness of all exposure control measures. Exposure controls for normal operating or routine procedures follow a tiered strategy. Engineering controls are the preferred means of long-term or permanent exposure control. If engineering controls are not feasible, appropriate use of personal protective equipment (PPE) may be considered as alternative control measures. Exposure controls for non-routine operations must be evaluated and addressed as part of the site-specific risk assessment.

RECOMMENDED PERSONAL PROTECTIVE EQUIPMENT (PPE):

Respiratory Protection:	Respiratory protective equipment (RPE) may be required for certain laboratory and large-scale manufacturing tasks if potential airborne breathing zone concentrations of substances exceed the relevant exposure limit(s). Workplace risk assessment should be completed before specifying and implementing RPE usage. Potential exposure points and pathways, task duration and frequency, potential employee contact with the substance, and the ability of the substance to be rendered airborne during specific tasks should be evaluated. Initial and ongoing strategies of quantitative exposure measurement should be obtained as required by the workplace risk assessment. All RPE must conform to local and regional specifications for efficacy and performance. Consult your site or corporate health and safety professional for additional guidance.
Skin Protection:	Gloves that provide an appropriate barrier to the skin are recommended if there is potential for contact with this material. Consult your site safety staff for guidance.
Eye Protection:	Safety glasses with side shields. Use of goggles or full face protection may be required based on hazard, potential for contact, or level of exposure. Consult your site safety staff for guidance.
Body Protection:	In small-scale or laboratory operations, lab coats or equivalent protection is required. Disposable Tyvek or other dust impermeable suit should be considered based on procedure or level of exposure. Use of additional PPE such as shoe coverings, gauntlets, hood, or head covering may be necessary. Consult your site safety staff for guidance. In large-scale or manufacturing operations, disposable Tyvek or other dust impermeable suit is recommended and based on level of exposure. Use of additional PPE such as shoe coverings, gauntlets, hood, or head covering may be necessary. Consult your site safety staff for guidance.

EXPOSURE LIMIT VALUES

See Occupational Exposure Guideline (OEG) listed above.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

FORM: Powder
COLOR: White
ODOR: Odor unknown
SOLUBILITY:
Water: Florfenicol: 1.32 mg/mL at pH7
Acetone: Florfenicol: Very soluble

See Section 5 for flammability/explosivity information.

SECTION 10. STABILITY AND REACTIVITY

STABILITY/ REACTIVITY:
Stable under normal conditions.

INCOMPATIBLE MATERIALS / CONDITIONS TO AVOID:
Open flames and high temperatures.

HAZARDOUS DECOMPOSITION PRODUCTS / REACTIONS:
Carbon oxides (COx).

SECTION 11. TOXICOLOGICAL INFORMATION

The information presented below pertains to the following individual ingredients, and not to the mixture(s).

ACUTE TOXICITY DATA

INHALATION:
Florfenicol: No mortality occurred in rats exposed to florfenicol for 4 hours at 0.28 mg/L (the maximum concentration tested). Clinical effects included dry rales, anogenital staining, secretory discharge, soft stool, and decreased body weights. These effects were seen immediately or up to one-week post exposure. Some effects did not resolve by study termination.

SKIN:
Florfenicol was not irritating to rabbit skin.

Povidone did not produce primary dermal irritation in a human repeated insult patch test.

EYE:
Florfenicol was slightly irritating to the eyes of rabbits.

Povidone did not produce ocular irritation in rabbits.

ORAL:
Florfenicol: Oral LD50: >2000 mg/kg (rat, mouse).
Dogs (one animal/sex) were administered successive oral doses of florfenicol that ranged from 160 to 1280 mg/kg. No clinical effects occurred at doses as high as 640 mg/kg. At 640 mg/kg, the only female died from inhalation of vomitus. Vomiting or soft stool occurred at 640 to 1280 mg/kg.

Lactose: Oral LD50: > 10g/kg (rat)

Povidone: (LD50 values vary based on molecular weight):
Rat (Oral) LD50: >100 g/kg (PVP K-30, molecular weight 40,000)
Rat (Oral) LD50: 8.25 g/kg (unspecified molecular weight)

DERMAL AND RESPIRATORY SENSITIZATION:
Florfenicol was not a skin sensitizer in guinea pigs.

Povidone did not produce sensitization in a human repeated insult patch test.

REPEAT DOSE TOXICITY DATA

SUBCHRONIC / CHRONIC TOXICITY:
Florfenicol was administered orally to dogs, rats, and mice at dosages as high as 100 to 400 mg/kg/day for up to 13 weeks. Effects including decreased body weight, changes in liver weight or liver enzyme levels, changes in testicular weight, testicular atrophy, decreased white blood cell counts, and decreased hemoglobin levels were observed at high dosages. Cellular changes in the liver or lymph nodes of rats and mice, and histopathologic changes in the brain and spinal cord of dogs were also noted at these high dosages. Although some effects were reversible after a 4-week withdrawal from treatment, testicular effects in rats persisted. Intramuscular injections of 45 mg/kg of florfenicol in swine produced diarrhea, injection site lesions, decreased body weight, decreased food and water consumption, changes in serum electrolytes and proteins, decreased red blood cell and white blood cell counts, decreased spleen weight, and decreased kidney weight.

In 52-week oral toxicity studies in dogs and rats, high dosages of florfenicol (12 and 48 mg/kg/day, respectively) increased liver weight and produced cellular changes in the gall bladder of dogs. In rats, florfenicol at the high dosage reduced body weight gain, reduced testicular weight, induced changes in hematologic and clinical chemistry parameters, and increased the incidence of testicular tubular atrophy. In two-year chronic studies in mice and rats, florfenicol caused similar effects as those observed in other long-term studies including reduced body weight gain, reduced red blood cell count, reduced hemoglobin levels, and testicular effects such as small testes, tubular atrophy and aspermatogenesis in both the high dosage rats (48 mg/kg/day) and mice (200 mg/kg/day).

Povidone fed to rats and dogs at 10% in the diet for 90 or 28 days, respectively, had no effect in rats; in dogs it increased spleen weight and accumulated in the mesenteric lymph nodes.

REPRODUCTIVE / DEVELOPMENTAL TOXICITY:
In a two-generation reproductive study, oral administration as high as 12 mg/kg/day of florfenicol reduced epididymal weights, decreased pup survival, and reduced lactation index in rats [NOAEL: 3 mg/kg/day].

There was no evidence of teratogenicity in rats administered florfenicol at dosages of 4, 12 or 40 mg/kg/day. Slight maternal toxicity, evidenced by decreased food and water consumption, was observed above 4 mg/kg/day. At 40 mg/kg/day, an increased incidence of delayed ossification and decreased fetal weight occurred. The NOAEL for maternal and fetal toxicity in rats was determined to be 4 mg florfenicol/kg/day.

Two teratogenicity studies were performed in mice. In the first study, the mice were administered florfenicol at dosages of 40, 120, or 400 mg/kg by gavage on days 6-15 of gestation. Florfenicol produced embryolethality at the 400 mg/kg/day dose level, which was evidenced by the high incidence of intrauterine deaths. Significant decreases in mean fetal body weight, soft tissue defects, and retarded skeletal ossification were also observed at 400 mg/kg/day. Skeletal ossification was less pronounced, in a dose-related fashion, at the lower doses tested (40 and 120 mg/kg/day). A developmental NOAEL could not be determined for these data [NOAEL for maternal: 120 mg/kg]. In the second teratogenicity study, florfenicol was retested at lower administered dosages of 1, 3, or 60 mg/kg/day. Maternal effects were limited to a slight increase in water consumption at the 60 mg/kg/day dose. There was no evidence of any adverse effects on the embryo/fetus at doses as high as 60 mg/kg/day in this study. However, based upon the retarded skeletal ossification effects observed in the first study at 40 mg/kg/day the NOAEL for the two studies combined was determined to be between 3 and 40 mg/kg/day.

Pregnancy rate and fetal parameters were unaffected in rabbits given povidone at 1250 mg/kg/day (IV), and in rats fed 10% povidone in the diet.

MUTAGENICITY / GENOTOXICITY:
Florfenicol was negative in a bacterial mutagenicity study (Ames), a mammalian mutagenicity study (mouse lymphoma), a bone marrow micronucleus assay, an in vitro chromosomal aberration assay in CHO cells, a cytogenetics assay in bone marrow, and an unscheduled DNA synthesis assay in rat hepatocytes.

Povidone was negative in a bacterial mutagenicity study (Ames), mammalian mutagenicity study (mouse lymphoma), mouse dominant lethal assay, chromosomal aberration assay, and BALB/C3T3 transformation assay.

CARCINOGENICITY:
Florfenicol was not carcinogenic in a 2-year study in rats administered dosages up to 48 mg/kg/day for 5 days a week or in mice at dosages up to 200 mg/kg/day for 5 days per week.

SECTION 12. ECOLOGICAL INFORMATION

There are no data for the final product or its formulation(s). The information presented below pertains to the following ingredient(s).

ECOTOXICITY DATA

INGREDIENT ECOTOXICITY

Florfenicol: 96-hr LC50 (bluegill): >830 mg/L
Florfenicol: 96-hr LC50 (trout): >780 mg/L
Florfenicol: 48-hr EC50 (daphnid): >330 mg/L
Florfenicol: Algae maximum cell density: MIC = 1.5 mg/L
Florfenicol: Algae maximum growth rate: MIC >2.9 mg/L

ENVIRONMENTAL DATA

OTHER INGREDIENT ENVIRONMENTAL DATA:

Florfenicol: log Pow (log octanol/water partition coefficient): 2.36
Florfenicol: Solubility 1.32 mg/ml at pH 7
Florfenicol: Biodegrablity: Not readily biodegradable but there is evidence of inherent biodegradability.

ENVIRONMENTAL FATE AND EFFECTS:
Photolytic half-life of Florfenicol in synthetic humic water (SHW) or pure water (PW) was 196 days in SHW and 171 days in PW.

SECTION 13. DISPOSAL CONSIDERATIONS

MATERIAL WASTE:
Disposal must be in accordance with applicable federal, state/provincial, and/or local regulations. Incineration is the preferred method of disposal, when appropriate. Operations that involve the crushing or shredding of waste materials or returned goods must be handled to meet the recommended exposure limit(s).

PACKAGING AND CONTAINERS:
Disposal must be in accordance with applicable federal, state/provincial, and/or local regulations.

SPECIAL ENVIRONMENTAL HANDLING PROCEDURES:
This product contains materials that are harmful to the environment. Do not allow product to reach ground water, water courses, sewage or drainage systems.

SECTION 14. TRANSPORT INFORMATION

This material is not subject to the transportation regulations of DOT, IATA, IMO, and the ADR.

SECTION 15. REGULATORY INFORMATION

TSCA LISTING

INGREDIENT	TSCA
Lactose	X
Povidone	X

U.S. STATE REGULATIONS

INGREDIENT	California Proposition 65	CARTK	NJRTK	CTRTK	MARTK
Povidone		X			

Fields in the above tables that do not contain data indicate that those materials have not been listed by local regulations.

SECTION 16. OTHER INFORMATION

Although reasonable care has been taken in the preparation of this document, we extend no warranties and make no representations as to the accuracy or completeness of the information contained therein, and assume no responsibility regarding the suitability of this information for the user's intended purposes or for the consequence of its use. Each individual should make a determination as to the suitability of the information for their particular purpose(s).

The brand-names or trademarks indicated by CAPITAL LETTERS in this [M]SDS are the property of, licensed to, promoted or distributed by Merck & Co., Inc., its subsidiaries or related companies.

DEPARTMENT ISSUING MSDS:
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(908) 473-3371 (Worldwide)
Monday to Friday, 9am to 5pm (US Eastern Time)

MSDS CREATION DATE: 12-Nov-1992

SUPERSEDES DATE: 21-Mar-2008

SECTIONS CHANGED (US SUBFORMAT): 1, 16
SIGNIFICANT CHANGES (US SUBFORMAT): Phone Number(s), OEB

Form FFC-W. Worksheet for Designing Individual Field Trials under Aquaflor® INAD #10-697

INSTRUCTIONS

1. This Worksheet is an aid for Investigators preparing to use Aquaflor® under INAD #10-697. The information solicited is required to comply with FDA regulations. Before beginning, Investigators should have carefully read through the entire Study Protocol. Fill in this Worksheet as completely as possible.
2. Investigators should keep one copy on file, and send another copy to the Monitor for review and signature. The Monitor should then forward the signed Worksheet to the Study Director. The Study Director will also review the Worksheet, assign the Worksheet a Study Number, and then provide the Investigator and Monitor with the Study Number and approval to proceed with Aquaflor® treatment.

SITE INFORMATION

Facility			
Address			
Investigator			
Reporting Individual (if not Investigator			
Phone		Fax	

FISH CULTURE AND DRUG TREATMENT INFORMATION

Fish species to be treated			
Fish species/stock to be treated			
Number of fish per unit (indicate tank, raceway or pond)			
Number of units to be treated		Number of untreated control units	
Average fish per pound		Estimated total weight of fish treated	
Intended florfenicol dosage (i.e., 10 or 15 mg florfenicol per kg fish per day)			
Projected % body weight to be fed			
Planned duration of drug treatment (days)			
Total medicated feed needed (lbs or Kg)			
Planned grams of Aquaflor® pre-mix in feed			
Anticipated treatment dates (start/end)			
Feed type (manufacturer/moist vs dry/size) for treatments and controls (identify both if different)			

STUDY DESIGN: Variable(s) to be tested: (See Sections VIII - XIII in Study Protocol). Describe in detail the purpose of the clinical trial (hypothesis), the number of experimental units, florfenicol dosage, the number of fish per unit, and the disease to be treated. Study designs must be carefully prepared and lend themselves to rigorous evaluation. If more space is required to describe study design, title additional page(s) "Study Design" and attach to this Worksheet.

Study designed by; _____

☐ **Note**: If proposed treatment is at a dosage of ***15 mg florfenicol/kg body weight/day for 10 consecutive days to control mortality caused by bacterial coldwater disease*** please check box to indicate that signed documentation from a licensed veterinarian verifying the need for treatment is attached to this Worksheet.

DISPOSITION OF TREATED FISH (Human Food Safety Considerations):

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

Check applicable box(es):

☐ 10 or 15 mg florfenicol per kg BW per day for 10 days; 21-day withdrawal period for salmonid species.

☐ 10 or 15 mg florfenicol per kg BW per day for 10 days; 28-day withdrawal period for non-salmonid species.

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

WORKER SAFETY CONSIDERATIONS:

_____ Initial here to indicate that all personnel handling drug have read Material Safety Data Sheet for Aquaflor® and are aware of SAFETY precautions to be taken when handling medicated feed.

Date Prepared: _____ **Investigator:** _____

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

FORM FFC-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 FFC-1 **immediately** upon receipt of florfenicol-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 Bozeman NIO.
4. **Note:** Both Investigator and Study Monitor should sign and date Form FFC-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. The following information is submitted in triplicate:

Name of Drug	**Aquaflor®**	INAD Number	**10-697**
Proposed Use of Drug	Treatment of certain bacterial diseases that occur in a variety of fish species		
Date of CVM Authorization Letter	September 17, 2007		
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	10-697		
Approximate dates of trial (start/end)			
Species, Size, and Type of Animals			
Maximum daily dose and duration	15 mg florfenicol/kg fish per day for 10 consecutive days		
Methods(s) of Administration	Medicated-feed		
Withdrawal Period	21 days for salmonid species; 28 days for non-salmonid species		

[1] To be filled out by the NIO

Date Prepared: _____ **Investigator:** _____

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

Date Reviewed: _____ **Sponsor:** _____

Form FFC-2a. Chemical Use Log for Clinical Field Trials Using Aquaflor® as a Feed Additive Under INAD #10-697 - Aquaflor® Premix

INSTRUCTIONS

1. Initiate Form 2 immediately upon receipt of Aquaflor® premix.
2. Each lot number of Aquaflor® premix may be used for multiple treatment regimes.
3. A signed copy of Form 2 should be sent to the Study Monitor at the end of the Study Year.
4. Original Form 2 should be archived at the investigating facility.

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

Aquaflor® Premix Lot Number	Date Received	Amount Received (ml)	Date Used	Study Number	Amount Aquaflor® Premix used for treatment (g)	Aquaflor® Premix Shipped[1] (g)	Aquaflor® Premix Disposal[2] (g)	Aquaflor® Premix on hand (g)	Inventory by (initials)

[1] Unused Aquaflor® Premix that is shipped to another facility participating in Aquaflor® INAD #10-697 (**Note**: Aquaflor® Premix can only be shipped to another facility with prior authorization by the AADAP Office).

[2] Unused Aquaflor® Premix that is disposed of by burial or in a landfill.

Investigator: _____ **Study Monitor:** _____

Signature and Date Signature and Date

Form FFC-2b. Chemical Use Log for Clinical Field Trials Using Aquaflor® as a Feed Additive Under INAD #10-697 - Aquaflor® Medicated Feed

INSTRUCTIONS

1. Initiate Form 2 immediately upon receipt of Aquaflor® treated feed.
2. Each lot number of Aquaflor® treated feed should be used for a single treatment regime.
3. A signed copy of Form 2 should be sent to the Study Monitor at the end of the Study Year.
4. Original Form 2 should be archived at the investigating facility.

Qty of on hand from
previous page (ml) _____Facility _____Reporting individual_____

Aquaflor® Treated Feed Lot Number and % Premix	Date Received	Amount Received (lbs)	Date Used	Study Number	Aquaflor® Treated Feed Used for Teatment (lbs)	Aquaflor® Treated Feed Shipped[1] (lbs)	Aquaflor® Treated Feed Disposal[2] (lbs)	Aquaflor® Treated Feed On-hand (lbs)	Inventory by (initials)

[1] Unused Aquaflor® Premix that is shipped to another facility participating in Aquaflor® INAD #10-697 (**Note**: Aquaflor® treated feed can only be shipped to another facility with prior authorization by the AADAP Office).

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

Investigator: _____ **Study Monitor:** _____

Signature and Date Signature and Date

Form FFC-3. Diagnosis, Treatment, and Mortality Record for Clinical Field Trials Using Aquaflor® as Feed Additive under INAD #10-697

INSTRUCTIONS

1. Fully fill out this report no later than 10 days after completion of the 21-day post-treatment observation period. Attach lab reports and other information.
2. Investigator should sign the form, and archive the original in station files. Send a copy of the form to the Monitor. Within 10 days of receipt, the Monitor should send a copy to the Study Director for inclusion in the permanent file.

SITE INFORMATION

Facility	
Reporting Individual	

FISH CULTURE AND DRUG TREATMENT INFORMATION

Fish species treated		Fish disease treated	
Average fish/pound		Average fish length	
Number of fish per experimental unit (indicate tank, raceway, or pond)			
Number of treated units		Number of control units	
Total weight of fish treated (lbs or kg)		Feed rate (% BW/day)	
Treatment duration	10 days	Total medicated feed fed (lbs or kg)	
Aquaflor® lot number		Florfenicol dosage (i.e., 10 or 15 mg per kg fish body weight)	
Aquaflor® premix used to prepare medicated feed (g)			
Feed type (manufacturer/moist vs dry/size)			
Feeding method (hand, auto, demand)			
Preparation of Aquaflor® treated feed (top-dressed at facility or prepared by feed manufacturer)			
Date treatment started		Date treatment ended	

WATER QUALITY PARAMETERS

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

Form FFC-3. Daily Mortality Record

INSTRUCTIONS

Enter today's date (mo/day) and water temp (°F.). Enter the rearing unit numbers at the head of each column for each test or control unit in the study. Enter "T" if the unit is designated in the study to receive treatment. Enter "C" if the unit is designated as an untreated control unit. Also enter the number of fish in each rearing unit at the start of the study. Enter each days total mortality for each unit in the proper column. Use additional copies of this form for additional rearing units or additional days of observation.

			Rearing Unit #	Rearing Unit #	Rearing Unit #	Rearing Unit #	Rearing Unit #	Rearing Unit #	
		T or C							
		# Fish							
Day	Date	Water Temp	Mortality #	Mortality #	Mortality #	Mortality #	Mortality #	Mortality #	Observer Initials
Pre-treatment Period									
10									
9									
8									
7									
6									
5									
4									
3									
2									
1									
Treatment Period									
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									

Form FFC-3. Daily Mortality Record

INSTRUCTIONS

Enter today's date (mo/day) and water temp (°F.). Enter the rearing unit numbers at the head of each column for each test or control unit in the study. Enter "T" if the unit is designated in the study to receive treatment. Enter "C" if the unit is designated as an untreated control unit. Also enter the number of fish in each rearing unit at the start of the study. Enter each days total mortality for each unit in the proper column. Use additional copies of this form for additional rearing units or additional days of observation.

			Rearing Unit #	Rearing Unit #	Rearing Unit #	Rearing Unit #	Rearing Unit #	Rearing Unit #	
		T or C							
		# Fish							
Day	**Date**	**Water Temp**	**Mortality #**	**Mortality #**	**Mortality #**	**Mortality #**	**Mortality #**	**Mortality #**	**Observer Initials**
Post-treatment Period									
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									
21									

RESULTS: Explain outcome of treatment. Describe in detail exactly how treatment worked. Was treatment successful? If not, why not? Attach pathology reports; Both Pre-and Post-Treatment.

TOXICITY OBSERVATIONS: (Report any negative reaction of fish; did treatment harm fish?)

DRUG DISCHARGE RESULTING FROM TREATMENT: Calculate actual FFC drug level in hatchery discharge resulting from treatments. Use Addendum 2: Discharge Worksheet for calculations and attach completed Discharge Worksheet to this form. Also indicate method of disposal (if any) of FFC-bearing solid wastes.

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

☐ 21 day withdrawal period for salmonid species.

☐ 28 day withdrawal period for non-salmonid species.

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 UNUSED OR SPOILED AQUAFLOR® TREATED FEED:

☐ **NEGATIVE REPORT:** Aquaflor® treated feed was not used at this facility under this Study Protocol Number. (Investigator should initial for negative reports.)

Date Prepared: _____ **Investigator:** _____

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