STUDY PROTOCOL FOR A COMPASSIONATE AQUACULTURE INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR ERYTHROMYCIN (Erymicin 200 Injection) (INAD 12-781)

Sponsor:

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

_____ _____

Sponsor Signature Date Approved

Manufacturer/Source of Supply:

Western Chemical, Inc.
1269 Lattimore Road
Ferndale, WA

Office for Coordination of Erythromycin (Erymicin 200 Injection) INAD:

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

Proposed Starting Date	July 1, 2016
Proposed Ending Date	July 31, 2020
Study Director	Ms. Bonnie Johnson

Clinical Field Trial Location:

Facility: _____

Investigator: _____

STUDY PROTOCOL FOR A COMPASSIONATE AQUACULTURE INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR ERYTHROMYCIN (Erymicin 200 Injection) UNDER INAD 12-781

I. STUDY ID AND TITLE

Clinical field trials to determine the efficacy of erythromycin (Erymicin 200 Injection) treatment to 1) control mortality caused by bacterial kidney disease (BKD; causative agent: *Renibacterium salmoninarum*) in a variety of salmonid species; and 2) to control (prevent) the vertical transmission *of R. salmoninarum* from BKD positive female salmonid broodstock to eggs/progeny. INAD 12-781.

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; Email: dave_erdahl@fws.gov

Manufacturer/Source of Supply:

Western Chemical, Inc.
1269 Lattimore Road
Ferndale, WA

Contact: Dr. Jim Brackett
1269 Lattimore Road
Ferndale, WA

Phone: 250-752-5256
Email: brackett@syndel.com

Note: Erymicin 200 Injection is a product of **Jurox Pty Limited**, 85 Gardiner Street, Rutherford NSW 2320, Australia

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

INAD Study Monitors: See Appendix II for names and contact information.

III. INVESTIGATORS/FACILITIES

See Appendix IIIa for names and contact information.

IV. PROPOSED STARTING AND COMPLETION DATES:

Proposed Starting Date: July 1, 2016

Proposed Completion Date: July 31, 2020

V. BACKGROUND/PURPOSE

Bacterial Kidney Disease (BKD) is a systemic infection found to occur in both wild and cultured salmonids. Although BKD more typically results in chronic mortality over an extended period of time, it can also cause acute, high-level mortality. The disease is oftentimes slow to become evident, but very difficult to control and virtually impossible to eradicate completely. BKD was first reported in the United States in 1935 (Belding and Merrill, 1935). Although it was initially thought to be limited to cultured fish populations, it was discovered in a wild population of brook trout in 1970 (Post, 1987). To date, BKD has been found in cultured and free-ranging salmonid populations throughout the United States. BKD is particularly prevalent among Pacific salmonids in the western U.S., where it has been a serious fish health problem for many years.

The causative agent of BKD is *Renibacterium salmoninarum*, a small, gram-positive (diplobacillus) bacterium. The bacterium is non-acid-fast, non-motile, and is usually found in pairs. *Renibacterium salmoninarum* is fastidious and slow growing, but can be cultured using specialized media containing L-cysteine and extended incubation. Optimal incubation temperature is 15^{o}C. As traditional culture methodology is not practical for the routine diagnosis of BKD, other techniques are more commonly used for identification of *Renibacterium salmoninarum* including: 1) observation of clinical signs and presence of gram-positive bacilli in tissues; 2) fluorescent antibody techniques (FAT); 3) enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR - confirmatory method). Currently, FAT and ELISA are the most commonly used diagnostic techniques for BKD.

BKD can be transmitted via horizontal transmission (i.e., fish to fish in the same water supply), as well as by vertical transmission through infected gametes (Evelyn et al, 1986; Brown et al, 1990; and Lee and Evelyn, 1994).
Routine surface disinfection of eggs with iodophor is an ineffective treatment as *Renibacterium salmoninarum* resides within the egg. Although water-hardening newly fertilized eggs with iodophor treatment may result in partial elimination of the pathogen and is commonly practiced, the overall utility of this methodology is considered variable.

External signs of BKD include hemorrhagic lesions on the body surface, subcutaneous abscesses which may result in open lesions, pimple-like blisters or nodules on the body surface,

and exophthalmia. External signs of BKD may commonly be limited to only a few fish in an infected population. Internal signs of BKD include swollen kidneys that often have a corrugated or "rope-like" appearance, white to gray-white cysts or abscesses in the kidney as well as the liver, spleen, and heart, and an accumulation of yellow-brown fluid in the body cavity. Fish with advanced BKD will have little or no visceral fat.

BKD has been found to be one of the more difficult bacterial diseases of fish to treat (i.e., control) with drugs or therapeutic agents. Not only is the disease chronic in nature and the pathogen widespread and egg transmissible, but the bacterium may be intracellular. Additionally, the pathogen has not been found to be highly susceptible to antibiotics commonly, and generally more effectively, used in fisheries management (Post, 1987). Although currently there are no FDA-approved treatments for the eradication of BKD, the disease can be controlled through treatment with antimicrobial compounds (Beitlich et al, 1995). Wolf and Dunbar, 1959 tested 34 therapeutic agents for the control of BKD, and found that only erythromycin resulted in significant control of mortality. Austin, 1985 evaluated 70 antimicrobial compounds (both *in vitro* and *in vivo*) for control of BKD in rainbow trout, and found that erythromycin was one of only 5 compounds potentially effective for use in early clinical cases.

Erythromycin is a macrolide antibiotic with bacteriostatic or bactericidal actions isolated from *Streptomyces erythreus* that is FDA-approved for use in both human and veterinary medicine. Although it is an effective antimicrobial for use against infections caused by a broad range gram-positive bacteria, it has little usefulness against staphylococcal and gram-negative bacteria (Moffit,1991). As most bacterial pathogens affecting aquatic species are gram-negative, the application of erythromycin therapy in aquaculture has been limited primarily to the treatment of BKD caused by *Renibacterium salmoninarum*. Although erythromycin is not approved for use in any aquatic species, experimental use (including under Investigational New Animal Drug exemption) for the treatment of BKD in Pacific salmonids has been both relatively widespread and effective. It has been used both as an injectable treatment, and as an oral (i.e., medicated feed) treatment. Injectable erythromycin has been used primarily to treat pre-spawning broodstock in order to minimize egg transmission of *Renibacterium salmoninarum*. Oral administration of erythromycin is believed to be the most effective (and practical) method of treating juvenile salmonids.

In recent years, numerous Federal, State, and Tribal hatcheries in the Pacific Northwest have relied heavily on erythromycin treatment of juvenile and adult salmonids to help meet critical management objectives. In the continuing struggle to restore/recover imperiled Pacific salmon stocks, erythromycin treatment has become an extremely important management tool to help mitigate the insidious impacts of BKD (Doug Munson, Idaho Fish and Game, personal communication).

The purpose of this compassionate INAD for erythromycin (Erymicin 200 Injection) is to: 1) provide fish culturists with another mechanism (i.e., in addition to erythromycin medicated feed INAD 6013 held by NRSP-7 and administered by the University of Idaho) to access and use erythromycin to control mortality caused by BKD, 2) provide fish culturists a mechanism to control (prevent) the vertical transmission of BKD from parents (broodstock) to eggs/progeny in a variety of salmonid species, and 3) develop clinical field trial and pivotal data demonstrating the efficacy and safety of erythromycin (Erymicin 200 Injection) treatment.

The USFWS anticipates that it may take several years to complete all technical section data requirements for a NADA for erythromycin (Erymicin 200 Injection). The USFWS is aware that opportunities for erythromycin (Erymicin 200 Injection) 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 and safety of erythromycin (Erymicin 200 Injection) 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 clinical field trial data demonstrating the efficacy and safety of erythromycin (Erymicin 200 Injection) treatment. These data will add to, and broaden, the database of publically available information on the efficacy and safety of erythromycin injection therapy.

2. Provide a new mechanism/opportunity for fishery biologists/fish culturists to legally access and use erythromycin (Erymicin 200 Injection) to 1) control mortality caused by bacterial kidney disease in a variety of salmonid species; and 2) to reduce or minimize *R. salmoninarum* levels in BKD positive female salmonid broodstock in order to control (prevent) the vertical transmission *of R. salmoninarum* to eggs/progeny.

Specifically, erythromycin (Erymicin 200 Injection) will be used in a variety of environmental conditions, at a range of water temperatures, and in a variety of cultured salmonid species to maintain healthy stocks of fish, until such time as a NADA for erythromycin (Erymicin 200 Injection) has been completed.

Within these two relatively broad objectives areas, there are two more specific study protocol objectives:

Objective A: To determine the efficacy and safety Erymicin 200 Injection treatment to control mortality caused by bacterial kidney disease in a variety of salmonid species; and

Objective B: To determine the efficacy and safety Erymicin 200 Injection treatment to reduce or minimize *R. salmoninarum* levels in BKD positive female salmonid broodstock in order to control (prevent) the vertical transmission *of R. salmoninarum* to eggs/progeny.

VII. MATERIALS

A. Test and control articles:

1. Drug Identity

a. Active ingredient

Common Name: Erythromycin

Product Name: Erymicin 200 Injection

Chemical Name: Erythromycin ($C_{37}H_{67}NO_{13}$)

CAS Number: 114-04-8

Appearance: Clear, light yellow liquid (not miscible with water)

Odor: None

b. Strength and dosage form: 200mg erythromycin per ml

c. Manufacturer, source of supply

Western Chemical, Inc.
1269 Lattimore Road
Ferndale, WA

Contact: Dr. Jim Brackett
1269 Lattimore Road
Ferndale, WA

Phone: 250-752-5256
Email: brackett@syndel.com

Note: Erymicin 200 Injection is a product of **Jurox Pty Limited**, 85 Gardiner Street, Rutherford NSW 2320, Australia

2. Verification of drug integrity/strength:

The Manufacturer, Jurox Pty Limited, will provide the analytical data necessary to establish the purity of each lot of Erymicin 200 Injection used for treatment under INAD 12-781. The lot number and date of manufacture for each batch of Erymicin 200 Injection 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 ERYMICIN-1) will clearly identify the lot number and date of manufacture

of Erymicin 200 Injection shipments. If the integrity of the Erymicin 200 Injection is compromised in any way (e.g., spilling, contamination, heat, etc.) the event will be carefully recorded, dated, and initialed in the Chemical Use Log (Form ERYMICIN-2). The Study Monitor assigned to the Investigator involved will be immediately notified.

3. Storage Conditions

Erymicin 200 Injection will be stored in the original container supplied by the Manufacturer with the appropriate investigational label attached. Erymicin 200 Injection will be stored in a dry, flame-proof storage unit, protected from light, and at temperatures below 30^{o}C. The storage unit should be kept locked at all times. Once opened, unused Erymicin 200 Injection product should be discarded after 28 days. Do not use if the remaining solution is not clear, colorless, and free from particulate matter. Erymicin 200 Injection should be stored at temperatures and for periods of time not to exceed limits set by the manufacturer.

4. Handling Procedures

Each Study Monitor and Investigator will be required to have a current copy of the Material Safety Data Sheet (MSDS) for Erymicin 200 Injection (see Appendix IV). Each person involved with the study and each person who may be present during the use of Erymicin 200 Injection shall be required to read the MSDS. Safety precautions as outlined in the MSDS will be followed at all times when working with Erymicin 200 Injection.

5. Investigational labeling

Copies of the labels to be attached to each container of Erymicin 200 Injection are provided in Appendix V. It is the responsibility of the Investigator to ensure proper labeling of all containers of Erymicin 200 Injection.

6. Accountability

Western Chemical, Inc. will be the sole supplier of Erymicin 200 Injection to all Investigators under INAD 12-781.

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

1. USFWS and Non-USFWS Facilities

Immediately upon receiving an order/shipment of Erymicin 200 Injection, the Investigator must complete Form ERYMICIN-1 “Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food

Animals". The investigator must then forward Form ERYMICIN-1 to the Study Director at the AADAP Office. The Study Director will in turn forward a copy to FDA.. Arrangements should be made between Investigators and Study Monitors to insure completed Form ERYMICIN-1s are received by the Study Director in a timely manner.

All Investigators are also responsible for maintaining an accurate inventory of Erymicin 200 Injection on-hand. A Chemical Use Log (Form ERYMICIN-2) must be completed and maintained by each Investigator. Each time Erymicin 200 Injection is used, it must be recorded by the Investigator on Form ERYMICIN-2.

7. Preparation Procedures

Erymicin 200 Injection will be supplied to Investigators in sterile 100 ml glass vials. Erymicin 200 Injection should not be adulterated in any manner prior to use. Erymicin 200 Injection should be administered by sterile syringe.

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 tissues and to 1) culture bacteria and identify culture growths microscopically using fluorescent antibody techniques, and 2) conduct enzyme-linked immunosorbent assays and Polymerase Chain Reaction (PCR) procedures. Syringes or other semi-automated injection systems (e.g., Rapidovacs) will be used for Erymicin 200 Injection administration.

When the Study Protocol has been approved and treatments are scheduled, the Investigator at each facility covered by the Erymicin 200 Injection INAD will need to complete several forms. These forms are described in Section XIII (p 14). 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 Erymicin 200 Injection 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.) are 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 ERYMICIN-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 (Objective A: Control of Mortality)

1. *Renibacterium salmoninarum* should be presumptively identified by procedures described in Section 1, Chapter 1 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 ERYMICIN-3 "Diagnosis and Treatment Record"**).

2. There should be an increased mortality rate among fish in at least one rearing unit 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 clinical disease signs must be detectable in at least a few fish and the causative agent (i.e., *Renibacterium salmoninarum*) should be identified.

4. Since the efficacy of Erymicin 200 Injection therapy for the control of mortality caused by BKD 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 Erymicin 200 Injection therapy. Complicating bacterial or other parasitic diseases should be carefully documented. If necessary, these infections can be treated once Erymicin 200 Injection response (efficacy) data has been collected. However,

it may take as long as 10 days after the completion of Erymicin 200 Injection therapy to determine differences between test and control groups and to complete post-treatment evaluations.

F. Pathogen/disease considerations (Objective B: Control of Vertical Transmission)

1. *Renibacterium salmoninarum* should be presumptively identified by procedures described in Section 1, Chapter 1 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 ERYMICIN-3 "Diagnosis and Treatment Record"**).

2. It is anticipated that the majority of Erymicin 200 Injection treatments under this INAD will be used to control (prevent) vertical transmission *of R. salmoninarum* from returning wildstock adult female salmonids to their progeny (i.e., not captive broodstocks). Therefore, historical Enzyme Linked Immunosorbent Assay (ELISA) or Real-time Polymerase Chain Reaction (RT-PCR) data that have quantitatively documented historical levels of *R. salmoninarum* in wildstock adult female broodstocks will be relied upon heavily to determine when treatment is warranted. In many cases, treatment will likely be initiated soon after adult females return to the hatchery or collection site.

3. Since the efficacy of Erymicin 200 Injection therapy to control (prevent) the vertical transmission of *R. salmoninarum* 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 Erymicin 200 Injection therapy. Complicating bacterial or other parasitic diseases should be carefully documented. However, it should be noted that it may take as long as 60-90 days after the completion of Erymicin 200 Injection 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 ERYMICIN-W: "Worksheet for Designing Individual Field Trials" that pertains to each specific treatment event. The worksheet should be filled out, electronically signed, and forwarded to the Study Monitor. The Study Monitor will review the planned treatment (worksheet), electronically sign it, and forward it to the Study Director at the AADAP Office. The Study Director will then review the worksheet, assign the approved treatment a Study Number, and then 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 ERYMICIN-2 and ERYMICIN-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 Study Director for a study number and permission to proceed.

Note: The INAD Program Management System (IPMS), which is an on-line database that must be used by Investigators for all INAD reporting, has a built-in system of checks, balances, and email notifications to ensure that all information/data reporting follows established INAD Study Protocol guidelines.

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 Erymicin 200 Injection treatment. Fish from a group or lot will first be examined to determine if treatment with Erymicin 200 Injection is warrented. 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 *Renibacterium salmoninarum* infection 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 new animal drug application.

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

Erymicin 200 Injection will be administered by injection treatment. Fish may receive either intramuscular or intraperitoneal injection.

B. Dose to be administered

Erymicin 200 Injection will be administered at a dosage of 10-25 mg erythromycin per kg of fish biomass per injection.

C. Dosing interval and repetition

Objective A (control mortality): Erymicin 200 Injection will be administered as a single treatment regime (injection), with no repetition of treatment.

Objective B (control/prevent vertical transmission): Erymicin 200 Injection will be administered as a single or multiple treatment regimen (injection), with a maximum of 3 treatments (injections). **Note**: each injection will be administered at a dosage of 10-25 mg erythromycin per kg fish biomass, and total dosage administered over the entire treatment period will not exceed 75 mg erythromycin per kg fish biomass. The interval between treatments (injections) must be a minimum of 21 days.

D. Duration of treatment

Not Applicable.

E. Drug preparation and administration procedures

Erymicin 200 Injection will be supplied from the manufacturer as a “ready to inject” product, and will require no further preparation by the Investigator. Erymicin 200 Injection contains 200 mg erythromycin per ml.

Standard personal protective equipment such as gloves, lab coats or aprons, eye protection, etc. should be worn at all times when preparing and administering Erymicin 200 Injection (see Appendix IV: MSDS for Erymicin 200 Injection)

F. Feeding Regime

As an injection treatment, Erymicin 200 Injection treatment should cause no significant disruption to normal feeding regime. However, and at the discretion of the Investigator, fish may be taken off-feed the day prior to handling and treatment.

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 Erymicin 200 Injection 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 Erymicin 200 Injection 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 ERYMICIN-3. Treatment response parameters that should be addressed include the following:

Objective A (control of mortality):

1. Primary Parameters

Morbidity and mortality data, coupled with case history and bacteriological analyses usually indicate when Erymicin 200 Injection treatment is needed. **This source data must be collected for at least 5 days before treatment, during treatment, and for at least 10 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 and bacterial load of *Renibacterium salmoninarum*.

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 erythromycin treatment has been used fairly extensively with beneficial effect

in salmonid culture, it is possible adverse reactions may occur under certain environmental conditions or with respect to specific species/strains of fish. Carefully observe all treated fish for any signs of any adverse reaction to treatment. The Investigator should carefully document all observations of adverse reactions. If any signs of drug toxicity are detected, they should also be documented and immediately reported to the Study Monitor, who will in turn notify the Study Director.

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

Objective B (control/prevention of vertical transmission):

1. Primary Parameters

The primary response variable will be the presence or absence of R. salmoninarum in adult females at the time of spawning. If *R. salmoninarum* is found, the "bacterial load" will also be quantified. Detection and bacterial load of R. salmoninarum will be will be determined by testing kidney samples using either Enzyme Linked Immunosorbent Assay (ELISA) or Real-time Polymerase Chain Reaction (RT-PCR). ELISA data should be reported as Optical Density (OD), and RT-PCR data should be reported as Cycle Threshold (CT). If using ELISA, a sample will be considered "positive" if it's OD is two standard deviations above the negative control. If using RT-PCR, a sample will be considered "positive" if it has a positive amplification of <40 CT. All *R. salmoninarum* data should be reported based on samples collected from individual fish.

2. Secondary Parameters

Morbidity and mortality data, coupled with case history and bacteriological analyses usually indicate when Erymicin 200 Injection treatment is needed. **This source data must be collected for at least 1 days before treatment, during treatment, and for at least 10 days after the treatment period has ended**. Collection of this data is critically important in all cases.

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 erythromycin treatment has been used fairly extensively with beneficial effect

in salmonid culture, it is possible adverse reactions may occur under certain environmental conditions or with respect to specific species/strains of fish. Carefully observe all treated fish for any signs of any adverse reaction to treatment. The Investigator should carefully document all observations of adverse reactions. If any signs of drug toxicity are detected, they should also be documented and immediately reported to the Study Monitor, who will in turn notify the Study Director.

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

XIII. FORMS FOR DATA COLLECTION

When the Study Protocol has been approved and treatments are scheduled, the Investigator at each facility covered by the Erymicin 200 Injection INAD will need to complete the following forms:

Form ERYMICIN-W.	Worksheet for Designing Individual Field Trials under INAD 12-781
Form ERYMICIN-1.	Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals
Form ERYMICIN-2.	Chemical Use Log for Clinical Field Trials Using Erymicin 200 Injection under INAD 12-781
Form ERYMICIN-3.	Results Report Form for use of Erymicin 200 Injection under INAD 12-781

Copies of these forms are attached to this Study Protocol. Actual reporting is accomplished on forms located on the INAD Program Management System on-line database.

XIV. RECORD KEEPING PROCEDURES

As stated immediately above, all data reporting are accomplished via forms located on the INAD Program Management System on-line database.

XV. DISPOSITION OF INVESTIGATIONAL ANIMALS

Objective A (control of mortality) and **Objective B** (control/prevention of vertical transmission):

Animals that die during treatment should be disposed of by burial or incineration. All fish treated with Erymicin 200 Injection must be maintained in culture facilities for a **minimum of 60 days** following completion of therapy and 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 ERYMICIN-3.

Objective B only:

Carcasses of salmon species that are treated within 60 days of spawning (i.e., death) **may not** be used for stream nutrient enhancement programs.

XVI. DISPOSITION OF INVESTIGATIONAL DRUG

Erymicin 200 Injection will be used only in the manner described, and by the individuals specified in the Study Protocol. If any unused or expired Erymicin 200 Injection 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 Erymicin 200 Injection. 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 Erymicin 200 Injection 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 7).

D. Administrator of the drug

Erymicin 200 Injection will be administered directly by the assigned Investigator (typically a fish hatchery manager) or under the Investigator's direct supervision (see Appendix IIIa for names). Erymicin 200 Injection 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 ERYMICIN-W, ERYMICIN-1, ERYMICIN-2, and ERYMICIN-3 (page 14) 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, and must complete all required data forms (see Section XIII on page 8). The Investigator should forward all completed forms to the Study Monitor for review. Study Monitors should carefully check each set of data for accuracy and completeness. If a form is incomplete or inaccurate, it should be returned to the Investigator. If a form is complete and accurate, it should be forwarded to the Study Director at the AADAP Office.

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 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 new animal drug application.

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**. Deviations should be documented on Form ERYMICN-3 in the *Description of Results* section.

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Post, G. 1987. Textbook of Fish Health. T.F.H. Publications, Inc. Neptune City, NJ. 288pp.

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ISSUED: 7 April 2016

SAFETY DATA SHEET

Section 1: IDENTIFICATION of CHEMICAL PRODUCT and COMPANY

Product Name:	**Erymicin 200 Injection**
Product Code:	502090 (100 mL)
Recommended Use:	An injectable antibiotic for the treatment of organisms sensitive to erythromycin in cattle, sheep, lambs and pigs.
Restrictions on Use:	For animal treatment only.
Company Identification:	Jurox Pty Limited
Address:	85 Gardiner Street, Rutherford, NSW 2320, Australia
Email:	jenq@jurox.com.au
Customer Centre:	1800 023 312
National Poisons Information Centre:	13 1126 (Australia-wide)
Emergency Telephone Number:	1800 023 312 (9am – 5pm, Monday to Friday)

Section 2: HAZARDS IDENTIFICATION

Hazard Classifications: This product has been assessed according to GHS and is classified as follows:

GHS Category	Hazard code	Hazard Statement
Flammable Liquid Category 2	H225	Highly flammable liquid and vapour
Eye Irritation Category 2A	H319	Causes serious eye irritation
Respiratory Sensitizer Category 1	H334	May cause allergy or asthma symptoms or breathing difficulties if inhaled
Skin Sensitizer Category 1	H317	May cause an allergic skin reaction

Signal word: DANGER

GHS Pictograms:

Flame | Health Hazard | Exclamation mark

Precautionary statements:

Prevention
P210 Keep away from heat/sparks/open flames/hot surfaces. - No smoking.
P233 Keep container tightly closed.
P241 Use explosion-proof electrical equipment.
P242 Use only non-sparking tools.
P243 Take precautionary measures against static discharge.
P280 Wear protective gloves and eye protection.

P264 Wash hands thoroughly after handling.
P261 Avoid breathing vapours.
P285 In case of inadequate ventilation wear respiratory protection.
P272 Contaminated work clothing should not be allowed out of the workplace.

Response
P303 + P361 + P353 IF ON SKIN (or hair): Remove immediately all contaminated clothing. Rinse skin with water/shower.
P333 + P313 If skin irritation or rash occurs: Get medical advice.
P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P337 + P313 If eye irritation persists: Get medical advice/attention.
P304 + P341 IF INHALED: If breathing is difficult, remove victim to fresh air and keep at rest in a position comfortable for breathing.
P342 + P311 If experiencing respiratory symptoms: Call a POISON CENTRE or doctor.
P363 Wash contaminated clothing before reuse.

Storage
P403 + P235 Store in a well-ventilated place. Keep cool.

Disposal
P501 Dispose of unused product in accordance with local regulations. Dispose of empty container by wrapping with paper and placing in garbage.

Section 3: COMPOSITION / INFORMATION on INGREDIENTS

INGREDIENT	CAS No.	CONTENT
Erythromycin	114-07-8	20%
Ethyl acetate	141-78-6	10 – 30%
Ethanol	64-17-5	< 40%
Ingredients not contributing to the hazards	-	10 – 30%

Section 4: FIRST AID MEASURES

General Information: Never give fluids or induce vomiting if a patient is unconscious or convulsing regardless of cause of injury. If medical advice/attention is needed, have this SDS, product container or label at hand.

Symptoms and Effects of Exposure: Symptoms and effects of exposure will be the same as for alcohol intoxication - impaired vision, co-ordination and reaction time, emotional instability, slurred speech, confusion, inco-ordination, disturbances in perception and senses, possible blackouts, flushing, fast heart rate, sweating and incontinence. Central nervous system depression may progress to coma.

Inhalation: If fumes, aerosols or combustion products are inhaled remove from contaminated area. If respiratory symptoms occur, remove patient to fresh air. Lay patient down and keep warm and rested. If breathing is shallow or has stopped, ensure airway is clear and apply resuscitation. If breathing is difficult, give oxygen and seek medical assistance immediately.

Ingestion: IF SWALLOWED, DO NOT INDUCE VOMITING. For advice, contact a Poisons Information Centre or a doctor. Give water to rinse out mouth, then provide liquid slowly and as much as casualty can comfortably drink. Never give liquid to a person showing signs of being sleepy or with reduced awareness; i.e. becoming unconscious. If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain open airway and prevent aspiration. Observe the patient carefully.

Injection: Treat as for needle stick injury. Wash area well and disinfect. If other symptoms become evident, seek medical advice.

Skin: If skin contact occurs: Immediately remove all contaminated clothing, including footwear. Flush skin and hair with running water (and soap if available). Seek medical attention in event of irritation.

Eye: If eye contact occurs: Immediately flush the eye continuously with running water. Ensure complete irrigation of the eye by keeping eyelids apart and away from eye and moving the eyelids by occasionally lifting the upper and lower lids. Continue flushing for at least 20 minutes. If eye irritation persists, get medical advice/attention.

Recommended First Aid Facilities: Ready access to running water and soap is required. Accessible eyewash is required.

Section 5: FIRE FIGHTING MEASURES

Flash Point: < 0.0°C

Hazardous Combustion Products: If involved in a fire, may emit noxious and irritant fumes.

Extinguishing Media: There is no restriction on the type of extinguisher which may be used. Use extinguishing media suitable for surrounding area.

Protective Equipment: Protective gloves and breathing apparatus.

HAZCHEM Code: •3YE

Section 6: ACCIDENTAL RELEASE MEASURES

Spills and Disposal: Exclude non-essential people from the area. Remove all ignition sources. Wear gloves, safety glasses / goggles and appropriate protective clothing. For small spills, clean up spilled product then wipe area and put empty container in garbage. For large spills, Prevent spillage from entering drains or water courses and call emergency services.

Protective Clothing: For appropriate personal protective equipment see section 8.

Environmental Precautions: Prevent from entering drains, waterways or sewers. If spill does enter waterways contact local authority.

Section 7: HANDLING AND STORAGE

Handling: Avoid accidental self-injection. Avoid contact with skin, eyes and inhalation of vapours. Use personal protective equipment as required. Do not eat, drink or smoke while handling product. Wash hands after use.

Storage: Keep out of reach of children. Store below 30ºC (room temperature). Protect from light. Store in flame-proof area.

Other Information: Avoid contact with incompatible substances as listed in Section 10. Always read the label before use.

Section 8: EXPOSURE CONTROLS/PERSONAL PROTECTION

This SDS describes personal protective measures relating to long term industrial and manufacturing exposure and emergency situations, such as accidents and spills. See product label for personal protective measures during normal use of the marketed product.

Exposure Limits: No exposure limits have been assigned for this product. Known exposure limits for ingredients are as follows:

Occupational Exposure Limits (OEL):

INGREDIENT	Source	TWA	STEL
Ethyl acetate	Australian Exposure Standards	720mg/m^3 / 200ppm	1440mg/m^3 / 400ppm
Ethanol	Australian Exposure Standards	1880mg/m^3 / 1000ppm	Not available

Emergency Limits:

INGREDIENT	TEEL-1	TEEL-2	TEEL-3
Ethyl acetate	400 ppm	400 ppm	10000 ppm
Ethanol	Not available	Not available	Not available

Engineering Controls: No special ventilation requirements are normally necessary for this product. However, minimise the creation of dusts and make sure that the work environment remains clean.

Personal Protective Equipment (PPE):

Eye protection: Protective glasses or goggles are recommended when handling bulk quantities of this product.

Skin protection: When handling bulk product, prevent skin contact by wearing chemical protective gloves e.g. PVC.

Respiratory protection: Not required for the normal use of this product.

Section 9: PHYSICAL AND CHEMICAL PROPERTIES

Appearance: Clear, light yellow liquid

Odour: Alcohol odour

Odour threshold: Not available

pH: Not available

Melting Point: Not available

Boiling Point: Not available

Flash Point: < 0.0°C

Evaporation Rate: Not available

Flammability: Highly flammable

Upper flammability limits: Not available

Lower flammability limits: Not available

Vapour Pressure: Not available

Vapour density: Not available

Relative density: Approx 0.98

Specific Gravity: Not available

Solubility in Water: Immiscible

Partition coefficient: Not available

Auto-ignition temperature: Not available

Decomposition temperature: Not available

Viscosity: Not available

Section 10: STABILITY AND REACTIVITY

Reactivity: This product is unlikely to react or polymerise under normal storage conditions.

Stability: When stored appropriately this product should show no significant degradation within the expiry period shown on the label.

Conditions to Avoid: Extreme temperatures. Heat, sparks, open flames, hot surfaces etc.

Incompatible Materials: Oxidising agents.

Hazardous Decomposition Products: No data available.

Section 11: TOXICOLOGICAL INFORMATION

Acute Toxicity:
Ingestion: No data for the mixture is available. Based on available data for the ingredients, the mixture is not considered to be acutely toxic by the oral route.

Erythromycin: Oral (mouse) LD_{50}: 2580 mg/kg;
Ethyl acetate: Oral (mouse) LD_{50}: 4100 mg/kg;
Ethanol: Oral (mouse) LD_{50}: 3450 mg/kg.

Inhalation: No data for the mixture is available. Based on available data for the ingredients, the mixture is not considered to be acutely toxic by the inhalation route.

Ethyl acetate: Inhalation (mouse) LC_{50}: 45,000 mg/m^3;
Ethanol: Inhalation (mouse) LC_{50}: 39000mg/m^3.

Dermal: No data for the mixture is available. Based on available data for the ingredients, the mixture is not considered to be acutely toxic by the dermal route.

Ethyl acetate: Dermal (mouse) LD_{50}: > 20 mL/kg;
Ethanol: Dermal (rabbit) LDLo: 20,000 mg/kg.

Injection:

Erythromycin: Subcutaneous (mouse) LD_{50}: 1800 mg/kg, Intramuscular (mouse): LD_{50} 394 mg/kg, Intraperitoneal (mouse) LD_{50}: 280 mg/kg, Intravenous (mosue) LD_{50}: 426 mg/kg;
Ethyl acetate: Subcutaneous (guinea pig) LD_{50}: 3000 mg/kg, Intraperitoneal (mouse) LD_{50}: 709 mg/kg;

Skin Corrosion / Irritation: No data for the mixture is available. Based on available data for the ingredients, the mixture is not considered to be a skin irritant. Due to the presence of ethanol and ethyl acetate, repeated exposure may cause skin cracking, flaking or drying following normal handling and use.

Serious Eye Damage / Irritation: No data for the mixture is available. Based on available data for the ingredients, the mixture is classified as an eye irritant. Ethyl acetate produces a high level of eye discomfort and is capable of causing pain and severe conjunctivitis. Corneal injury may develop, with possible permanent impairment of vision, if not promptly and adequately treated. Direct contact of the eye with ethanol (alcohol) may cause an immediate stinging and burning sensation, with reflex closure of the lid, and a temporary, tearing injury to the cornea together with redness of the conjunctiva. Discomfort may last 2 days but usually the injury heals without treatment.

Respiratory or Skin Sensitisation: No data for the mixture is available. Based on available data for the ingredients, the mixture is classified as both a respiratory sensitiser and a skin sensitiser. Exposure to erythromicin may induce hypersensitivity reactions in some individuals. Anaphylactic shock and skin rash may occur.

Germ Cell Mutagenicity: No data for the mixture is available. Based on available data for the ingredients, the mixture is not considered to be mutagenic.

Carcinogenicity: No data for the mixture is available. Based on available data for the ingredients, the mixture is not considered to be carcinogenic.

Reproductive Toxicity: No data for the mixture is available. Based on available data for the ingredients, the mixture is not considered to be a reproductive toxicant.

STOT: Single exposure: No data for the mixture is available. Based on available data for the ingredients, the mixture is not considered to be a specific target organ toxicant after single exposure.

STOT: Repeat exposure: No data for the mixture is available. Based on available data for the ingredients, the mixture is not considered to be a specific target organ toxicant after single exposure.

Aspiration hazard: Due to the presence of ethyl acetate, any material aspirated during vomiting may produce lung injury. Adverse effects of aspiration into the lungs may be delayed up to 48 hours.

Section 12: ECOLOGICAL INFORMATION

Ecotoxicity: Thiopentone sodium is harmful in the aquatic environment.

Fish
Thiopentone sodium: LC_{50} (96h): 26.2 mg/L.

Crustacea
No data.

Algae and other aquatic plants
No data.

Ingredient	Persistence: Water/Soil	Persistence: Air	Bioaccumulation	Mobility
Thiopentone sodium	No data	No data	No data	No data

Section 13: DISPOSAL INFORMATION

Product Disposal: Dispose of product only by using according to label or at an approved landfill.

Container Disposal: Dispose of container by wrapping with paper and placing in garbage.

Section 14: TRANSPORT INFORMATION

Dangerous Goods Classification: Classified as a Dangerous Good according to the criteria of the Australian Dangerous Goods (ADG) Code (land), the IATA Dangerous Goods Regulations (air) and the IMDG Code (sea).

Proper Shipping Name: FLAMMABLE LIQUID, N.O.S. (contains ethyl acetate and ethanol)

UN Number: 1993

Transport Hazard Class: 3

Packing Group: II

HAZCHEM Code: •3YE

Marine pollutant: NO

Section 15: REGULATORY INFORMATION

Poison Schedule (SUSMP): S4

APVMA No.: 52668

AICS: All of the significant ingredients in this formulation are compliant with NICNAS regulations.

Section 16: OTHER INFORMATION

This information is based on data believed by Jurox Pty Limited to be accurate at the time of writing but is subject to change without notice. It is given in good faith, but no warranty expressed or implied is made as to its accuracy, completeness otherwise and no assumption of liability from howsoever arising is made by Jurox Pty Limited by reason of the provision of this information. Every person dealing with the materials referred to herein does so at his/her own risk absolutely and must make independent determinations of suitability and completeness of information from all sources to ensure their proper use.

Legend:

ADG Code	Australian Dangerous Goods Code.
AICS	Australian Inventory of Chemical Substances.
CAS No.	Chemical Abstracts Service Registry Number.
EC_{50}	The median effect concentration, being a statistically derived concentration of a substance that can be expected to cause an adverse reaction in 50% of organisms or a 50% reduction in growth or in the growth rate of organisms.
GHS	Globally Harmonized System of Classification and Labelling of Chemicals.
Hazchem Code	Emergency action code of numbers and letters that provide information to emergency services especially firefighters.
IATA	International Air Transport Association.
IMDG Code	International Maritime Dangerous Goods Code.
KOC	Soil-Water Partition Coefficient. The ratio of a chemical's concentration that is adsorbed in the soil to the concentration of chemical in solution.
KOW	Octanol Water Partition Coefficient. The ratio of a compound's concentration in a known volume of n-octanol to its concentration in a known volume of water after the octanol and water have reached equilibrium.
LC_{50}	The median lethal concentration, being a statistically derived concentration of a substance that can be expected to cause death in 50% of animals.
LD_{50}	The median lethal dose, being a statistically derived single dose of a substance that can be expected to cause death in 50% of animals.
LDLo	Lethal Dose Low. The lowest published lethal dose.
NICNAS	National Industrial Chemicals Notification and Assessment Scheme.
NOEC	No-observable-effect-concentration.
N.O.S.	Not Otherwise Specified.
PPE	Personal Protective Equipment.
PVC	Polyvinyl chloride.
SDS	Safety Data Sheet.
STOT	Specific Target Organ Toxicity.
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons.
SWA	Safe Work Australia.

References:

ChemID Plus

EPA New Zealand Chemical Classification and Information Database (CCID)

HSDB (Hazardous Substances Data Bank)

This version issued: 7 April 2016 and is valid for 5 years from this date.

Supercedes: This SDS supercedes the version issued on 22 June 2011.

Revision History:

Date of Revision	Reason
7 April 2016	GHS classification and update of SDS to comply with SWA Code of Practice. Addition of flashpoint data.

END OF SDS

Form ERYMICIN-W: Worksheet for Designing Individual Field Trials Under Erymicin 200 Injection INAD 12-781

INSTRUCTIONS

1. Investigator must fill out Form ERYMICIN-W for each proposed treatment under this INAD before actual use of Erymicin 200 Injection.
2. Investigator should forward a copy of ERYMICIN Form-W to the Study Monitor for review.
3. After review, the Study Monitor should forward a copy to the AADAP Office for review and assignment of a Study Number.

SITE INFORMATION

Facility			
Address			
Investigator			
Reporting Individual (if not Investigator			
Phone		Email	

FISH CULTURE AND DRUG TREATMENT INFORMATION

Fish species to be treated			
Disease/pathogen to be treated		***BKD / Renibacterium salmoninarum***	
Treatment Objective A (control of mortality)			
Treatment Objective B (control/prevent vertical transmission via eggs)			
Average fish weight (gm)		Average fish length (in)	
Number of fish per rearing unit		Number of rearing units to be treated	
Total number of fish to be treated		Approximate water temperature	
Intended erythromycin dosage (10-25 mg/kg bw) per injection			
Number of injections		Injection interval (days)	
Anticipated date treatment will be initiated			
Anticipated treatment evaluation date			

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 FDA-mandated withdrawal times as described in the Study Protocol.

USE AND DISPOSITION OF ERYMICIN 200 Injection (Environmental Safety Considerations):

☐ Investigator should initial here to indicate awareness that Erymicin 200 Injection 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 Erymicin 200 Injection have read the Material Safety Data Sheet for Erymicin 200 Injection 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 ERYMICIN-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 ERYMICIN-1 **immediately** upon receipt of Erymicin 200 Injection.
2. Investigator should forward a copy of Form ERYMICIN-1 to the Study Director at the AADAP Office

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

Name of Drug	**Erymicin 200 Injection**	INAD Number	**12-781**
Proposed Use of Drug	Objective A: To control mortality caused by bacterial kidney disease in a variety of salmonid species Objective B: To control (prevent) the vertical transmission of Renibacterium salmoninarum via salmonid eggs		
Date of CVM Authorization Letter	08/11/2016		
Source of Drug	Western Chemical, Inc.		
Date of Drug Receipt		**Amount of Drug Received**	
Drug Lot Number			
Name of Investigator			
Address of Investigator			
Location of Trial			
Approximate Number of Treated Animals			
Study Protocol Number	12-781		
Approximate dates of trial (start/end)			
Species, Size, and Type of Animals			
Maximum daily dose and duration	25mg/Kg body weight		
Methods(s) of Administration	Injection (up to 3 injections)		
Withdrawal Period	60 days following completion of treatment		

[1] To be filled out by the AADAP Office

Investigator: _____ **Study Monitor:** _____

Signature and Date Signature and Date

Form ERYMICIN-2. Chemical Use Log for Clinical Field Trials Using Erymicin 200 Injection Under INAD 12-781

INSTRUCTIONS

1. Initiate Form ERYMICIN-2 immediately upon receipt of Erymicin 200 Injection.
2. Each lot number of Erymicin 200 Injection may be used for multiple treatment regimes.

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

Erymicin 200 Injection Lot Number	Date Received	Amount Received (ml)	Date Used	Study Number	Amount Erymicin 200 Injection used in treatment (ml)	Erymicin 200 Injection transferred[1] (ml)	Erymicin 200 Injection Disposal (ml)	Erymicin 200 Injection on hand (ml)	Inventory by (initials)

[1] Unused Erymicin 200 Injection that is shipped to another facility participating in Erymicin 200 Injection INAD 12-781 (Note: Erymicin 200 Injection can only be transferred to another facility with prior authorization by the AADAP Office).

[2] Unused Erymicin 200 Injection that is past expiry date or has been compromised should be disposed of in a lined-landfill.

Investigator: _____ **Study Monitor:** _____

Signature and Date Signature and Date

Form ERYMICIN-3: Results Report Form for Clinical Field Trials Using Erymicin 200 Injection Under INAD 12-781

INSTRUCTIONS

1. Investigator must fill out Form ERYMICIN-3 no later than 10 days after completion of treatment. Attach lab reports and other pertinent study information.
2. If Erymicin 200 Injection was not used under the assigned Study Number, contact the Study Director at the AADAP Office to close-out the study.
3. Investigator should forward a copy of Form ERYMICIN-3 to the Study Monitor. Within 10 days of receipt, the Study Monitor should forward a copy to the Study Director at the AADAP Office.

SITE INFORMATION

Facility	
Reporting Individual	

FISH CULTURE AND DRUG TREATMENT INFORMATION

Erymicin 200 Injection Lot Number		Total amount drug used (ml)	
Treatment **Objective A**		Treatment **Objective B**	
Fish species treated		Disease treated	**BKD/R. sal**
Average fish weight (gm)		Average fish length (in)	
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 treated fish			
Number of control rearing units		Number of fish per control rearing unit	
ID of all control rearing units (e.g. Tank 5, Pond 6B)			
Total number of control fish			
Treatment dosage (mg/kg)		Treatment date(s)	
Injection method (IM or IP)			
Number of injections		Injection interval (days)	
Evaluation date(s)		Evaluation interval (time from treatment until evaluation; days)	

Daily Mortality Record (use for treatments under both Objective A and Objective B)

INSTRUCTIONS

1. Investigator should fill out the Daily Mortality Record as completely as possible.
2. Prior to initiation of the trial, fill out Rearing Unit ID, whether a rearing unit is Treated or Control, and the number of fish in each rearing unit.
3. Use additional copies of this form if more than 6 rearing units are involved in the trial and/or the post-treatment period exceeds 21 days

FACILITY										
	Rearing Unit ID									
	Treated or Control									
	Number of Fish									
	Day	**Date**	**Water Temp (F°)**	**Mortality (# of fish)**	**Mortality (# of fish)**	**Mortality (# of fish)**	**Mortality (# of fish)**	**Mortality (# of fish)**	**Mortality (# of fish)**	**Daily Observer Initials**
Pre-Treatment Period	**5**									
	4									
	3									
	2									
	1									
Treatment Day(s)[1]										
	0									
Post: Treatment Period	**1**									
	2									
	3									
	4									
	5									
	6									
	7									
	8									
	9									
	10									
	11									
	12									
	13									
	14									
	15									
	16									
	17									
	18									
	19									
	20									
	21									

[1] If more than 1 treatment (injection) is used under Objective B, please note additional treatment date(s) on form

Renibacterium salmoninarum dectection in adult females at time of spawning (use only for treatments under Objective B)

INSTRUCTIONS

1. Investigator should fill out this form 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. Use additional copies of this form if more than 6 rearing units are involved in the trial and/or in order to include (report) data for all fish sampled.

FACILITY									
	Rearing Unit ID								
	Treated or Control								
	Number of Fish								
Fish #	Date sampled	ELISA orRT-PCR	Positive or Negative and OD or CT[1]	Positive or Negative and OD or CT	Positive or Negative and OD or CT	Positive or Negative and OD or CT	Positive or Negative and OD or CT	Positive or Negative and OD or CT	Daily Observer Initials

[1] OD = optical density from ELISA; CT = cycle threshold for RT=PCR

WATER QUALITY PARAMETERS

Mean treatment water temperature (^oF)		Dissolved Oxygen (mg/L)	
Hardness - $CaCO_3$ (mg/L)		pH	

RESULTS: Please describe treatment results in as much detail as possible. 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 **<u>any</u>** apparent drug toxicity that was observed during the study period, including a detailed description of unusual or abnormal fish behavior.

OBSERVED WITHDRAWAL PERIOD OF TREATED FISH:

Observed withdrawal period: _____ **60 days** Investigator should initial here to indicate compliance with established withdrawal period

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

DISPOSITION OF Erymicn 200 Injection

☐ Use and disposition of all Erymicin 200 Injection followed Study Protocol guidelines and has been clearly identified on Form ERYTHRO-2 (Investigator should initial)

☐ **NEGATIVE REPORT** Erymicin 200 Injection 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:** _____