STUDY PROTOCOL FOR A COMPASSIONATE AQUACULTURE INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR LUTEINIZING HORMONE-RELEASING HORMONE ANALOG des-Gly^{10},[D-Ala^{6}]LH-RH Ethylamide (LHRHa Liquid/LHRH$_a$) (INAD #8061)

Sponsor:

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

_____ _____
Sponsor Signature Date Approved

Manufacturer/Source of Supply:

Syndel USA
1441 W Smith Rd
Ferndale, WA 98248 USA

Office for Coordination of LHRHa Liquid/LHRH$_a$ INAD:

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

Proposed Starting Date	January 1, 1996
Proposed Ending Date	December 31, 2025
Study Director	Ms. Bonnie Johnson

Clinical Field Trial Location:

Facility: _____

Type or Print Name

Investigator: _____

Type or Print Name

_____ _____

Investigator Signature Date

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I. STUDY ID AND TITLE

Conduct clinical field trials to determine the efficacy of LHRHa Liquid/LHRH$_a$ to induce gamete maturation (ovulation and spermiation) in a variety of fish species. INAD #8061.

II. SPONSOR

Dr. Marilyn Blair, 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: marilyn_j_blair@fws.gov

Manufacturer/Source of Supply:

Syndel USA
1441 W Smith Rd
Ferndale, WA 98248 USA

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

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

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: January 1, 1996

Proposed Completion Date: December 31, 2025

V. BACKGROUND/PURPOSE

The use of hormones to induce spawning in fish is critical to the success of many U.S. Fish and Wildlife Service (USFWS) fisheries programs. A wide variety of programs, including several that involve the restoration of threatened/endangered species are dependent upon hormone treatment to complete final gamete maturation and ensure successful spawning.

The time of spawning is by its own nature a stressful period for all fish species. Both sexes are undergoing significant changes in physiology, morphology, and behavior (Hoar 1969). The handling required during the spawning of fish for artificial propagation complicates an already delicate situation. This is particularly true for wildstock species that must endure the added stresses of capture, handling, and confinement in an un-natural environment. The longer it is necessary to hold wild fish in captivity, the greater the likelihood of adversely affecting both the health of the fish and ultimate spawning success. In fact, with respect to some wildstock species, the stress of capture alone would be sufficient to cause complete reproductive failure unless spawning is induced by hormone treatment. Additionally, certain species have limited or depressed populations and in some cases may even be considered threatened/endangered. Hormone treatment of these fish is essential to ensure viable population numbers.

In order to maintain the health of both wildstock and domestic brood fish, it is beneficial to minimize overall fish handling. During the course of normal spawning operations at a hatchery, it may be necessary to handle and examine individual fish weekly over a 6-8 week period. Such procedures can be extremely stressful to valuable broodstocks, severely compromising general fish health. Successful hormone treatment can reduce handling requirements to a single hormone administration event followed by actual gamete collection, thereby greatly reducing overall fish handling.

Studies have shown that final gamete maturation (ovulation and spermiation) in fish can be induced by the administration of a variety of hormones (Donaldson and Hunter 1983; Goetz 1983). Recent investigations have found luteinizing hormone-releasing hormone analogues to be one of the most effective means of inducing final gamete maturation. These compounds are synthetic gonadotropin releasing hormones that are similar in structure to native luteinizing hormone-releasing hormones. Although a number of these analogues are available, the most commonly used analogue for fish culture is $LHRH_a$ (Alvarino et al. 1992; Donaldson et al. 1981; Erdahl and McClain 1987; Fitzpatrick et al. 1983; Taranger et al. 1992; and Van der Kraak et al. 1983). $LHRH_a$ is an attractive choice as it has both a high biological activity and low species specificity, making it appropriate for a variety of fish species (Coy et al. 1974). Although the use

of $LHRH_a$ as a tool to enhance broodstock spawning success is relatively new, it has already had a significant, positive impact on USFWS fisheries programs nationwide.

The purpose of this compassionate INAD for $LHRH_a$ is to develop clinical field trial data that will be used to determine the efficacy and appropriate treatment regimens for inducing ovulation and/or spermiation in a variety of cultured and wildstock fish species. These data will be used to support a new animal drug application (NADA) for $LHRH_a$.

USFWS anticipates requesting that FDA grant an extension of the $LHRH_a$ INAD for additional years at the end of this treatment season. The USFWS is aware that opportunities for $LHRH_a$ therapy are unpredictable. There is no way of knowing in advance if, when, or where opportunities for pivotal studies will be encountered. USFWS feels that data from at least three treatment seasons will be required in order to adequately assess the efficacy of $LHRH_a$ treatment on induced gamete maturation in fish to support a NADA.

VI. SPECIFIC OBJECTIVES

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

1. Collect scientific data necessary to establish the efficacy of LHRHa Liquid/$LHRH_a$ on gamete maturation in both cultured fish under typical hatchery situations and on critical wildstock species.

2. Provide the opportunity for USFWS fish culturists to legally use LHRHa Liquid/LHRHa to maintain the genetic integrity and improve the reproductive potential of hatchery broodstocks during the period of time necessary for collection of efficacy, safety, and residue data required for an NADA on LHRHa Liquid/LHRHa in fish. Specifically, LHRHa Liquid/LHRHa will be used to induce ovulation and spermiation in both domestic and wildstock populations, including several species that are listed under the Endangered Species Act.

VII. MATERIALS

A. Test and Control Articles:

1. Drug Identity

a. Active ingredient

Powder Formulation:

Common Name: Luteinizing Hormone-Releasing Hormone analogue

Chemical Name: des-Gly^{10},[D-Ala^{6}]LH-RH Ethylamide

CAS Number: 79561-22-1

Amino Acid Profile: (pGlu-His-Trp-Ser-Tyr-D-Ala-Leu-Arg-Pro-NHEt)

Appearance: White powder

Odor: Slight musty smell

Liquid Formulation:

Common Name: Luteinizing Hormone-Releasing Hormone analogue

Chemical Name: des-Gly^{10},[D-Ala^{6}]LH-RH Ethylamide

CAS Number: 79561-22-1

Amino Acid Profile: (pGlu-His-Trp-Ser-Tyr-D-Ala-Leu-Arg-Pro-NHEt)

Appearance: Clear liquid

Odor: None

b. Strength and dosage form

Powder Formulation:

$LHRH_a$ is a lyophilized powder distributed on a total weight basis. Peptide content is approximately 90%, with the balance being salts and water. It is available in vials containing either 1, 5, or 25 mg $LHRH_a$/vial. $LHRH_a$ should be diluted with physiological saline immediately prior to intended use. Dilution rate is dependent upon fish size, fish number, and intended dosage.

Liquid Formulation:

"LHRHa Liquid", is a sterile liquid form of LHRHa, and is available in a 100mL multi-use amber or clear vial. It is available at 80ug LHRHa per mL of solution, or 8mg per 100mL solution. The primary difference between "LHRHa Liquid" and the LHRHa lyophilized powder is that "LHRHa Liquid" has been reconstituted as a sterile liquid injectable under GMP conditions rather than by the end user.

c. Manufacturer, source of supply

Syndel USA
1441 W Smith Rd,
Ferndale, WA 98248 USA
Contact Person: Jason Montgomery
Phone: 800-283-5292
Fax: 360-384-0270

d. The use of LHRHa analog pellet implants is not authorized in food fish.

2. Verification of Drug Integrity/Strength:

The Manufacturer will provide the analytical data necessary to establish purity of each lot of LHRHa Liquid/$LHRH_a$ supplied. The lot number and date of manufacture for each batch of LHRHa Liquid/$LHRH_a$ 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 LHRHa Liquid/LHRHa - 1) will clearly identify the lot number and date of manufacture of $LHRH_a$ shipments. If the integrity of the LHRHa Liquid/LHRHa is compromised (i.e., by spilling or contamination of the stock container) the event will be carefully recorded, dated, and signed in the Chemical Use Log (Form LHRHa Liquid/LHRHa - 2). The Study Monitor assigned to the Investigator involved will be immediately notified.

3. Storage Conditions

Powder Formulation: Long term storage for LHRHa will be stored in the original container supplied by the Manufacturer with the appropriate INAD labeling attached. The container will be stored in a freezer that maintains a temperature of less than 0C. The freezer must be labeled to indicate that it contains hazardous material and that "**NO** Food or Drink is to be stored in this Refrigerator/Freezer". LHRHa should be stored in a secure location. Short term storage/shipping for $LHRH_a$ will be stored in the original container supplied by the Manufacturer with the appropriate INAD labelling attached. The container should be stored in a cool (2-8C) container out of direct sunlight.

Liquid Formulation: LHRHa Liquid will be stored in the original container (100mL amber or clear vial) supplied by the Manufacturer with the appropriate investigational label and information attached. The container will be stored in the refrigerator and shall **not be frozen**. The refrigerator must be labeled to indicate that it contains hazardous material and that "No Food or Drink is to be Stored in this Refrigerator/Freezer". LHRHa Liquid should be stored in a secure location.

4. Handling Procedures

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

5. Investigational Labeling

A copy of the label to be attached to each container of LHRHa Liquid/LHRHa is provided in Appendix V. Although investigational labels will be affixed to containers by the supplier, it is the responsibility of the Investigator to ensure proper labeling of all containers of LHRHa Liquid/LHRHa.

6. Accountability

Syndel USA will be the sole supplier of LHRHa Liquid/LHRHa to all Investigators under INAD 8061.

The Online INAD Database must be used by Investigators for ALL INAD reporting.

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

1. All facilities using LHRHa Liquid/LHRHa:

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

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

At the conclusion of the study, all remaining LHRHa Liquid/LHRHa will be destroyed by following the SDS (note: unless LHRHa Liquid/LHRHa is planned for use in another approved field trial, and planned usage is within the storage guidelines established by the manufacturer). Disposition of all LHRHa Liquid/LHRHa must be properly recorded and accounted for in the Drug Inventory Form of the database which is Form LHRHa Liquid/LHRHa -2. The Study Monitor will be responsible for verifying the quantity of LHRHa Liquid/LHRHa remaining on hand versus the amount indicated on Form LHRHa Liquid/LHRHa -2. **Note:** LHRHa Liquid/LHRHa can be transferred to other facilities that are participating under INAD 8061. Transfers must be shown in the Drug Inventory section of the database (formerly Form LHRHa Liquid/LHRHa -2).

7. Preparation Procedures

Powder formulation:

$LHRH_a$ for injection will be supplied in vials containing 1, 5, or 25 mg of a lyophilized white powder. Based on the relatively small amount of hormone per vial, investigators should not attempt to divide $LHRH_a$ into additional aliquots (unless a high quality analytical balance and a Good Laboratory Practice laboratory are available). Immediately prior to injection, $LHRH_a$ should be diluted using a sterile, physiological saline solution. Dilution volume is dependent upon dosage, size and number of fish to be injected, and desired injection volume.

Liquid formulation:

No preparation is required for the liquid formulation of LHRHa Liquid”. Use appropriate size needle and syringe for the species of fish being treated, and

calculate the volume to be administered based on the target dose (priming, resolving, or total) and the concentration of the LHRHa Liquid product, 80ug/mL.

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

Treatment equipment should include clean glassware, sterile physiological saline, and sterile syringes and needles. A compound microscope should be available for evaluation of sperm motility.

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

VIII. EXPERIMENTAL UNIT

The experimental unit in this clinical field trial may consist of a contained or isolated group of fish. This will generally be a group of fish contained in a tank, raceway, or pond. It could also be a group of fish held in confinement in a lake or stream. However, the experimental unit in this clinical field trial 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 this Study Protocol for the current calendar year before LHRHa Liquid/LHRHa 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 should arise (See Section XX). However, poor planning and/or a lack of preparation will not be considered an emergency situation.

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

C. Period of use

LHRHa Liquid/LHRHa treatment has been shown to be most effective when administered during the final stages of gamete maturation. In most cases, LHRHa Liquid/LHRHa will be used within 4 weeks of the time fish are normally expected to spawn.

D. Environmental conditions

Environmental conditions will be variable and include a broad spectrum of

temperatures a water quality parameters. Environmental conditions will be reported on Form LHRHa Liquid/LHRHa -3.

Since LHRHa Liquid/LHRHa activity is rapidly lost in dilute aqueous solution (Merck Index, 1989), there will be no drug discharge from participating facilities. Therefore, LHRHa Liquid/LHRHa qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.33(e). Drug discharge must be in compliance with local **NPDES** permitting requirements.

E. Ability of investigator to fulfill all the requirements of the Study Protocol

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

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

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

X. TREATMENT GROUPS

A. A treatment group or experimental unit may be an entire tank, pond, raceway, or group of fish. However, the experimental unit should be considered individual fish whenever possible.

B. Control groups will not be a requirement for clinical field trials evaluating the efficacy of LHRHa Liquid/LHRHa treatment. In some cases, particularly with respect to wildstock populations, the number of broodfish available at a given time for LHRHa Liquid/LHRHa treatment may be extremely limited. It is likely that some facilities may need to initiate treatment on groups of ten or fewer brood fish. To establish

meaningful control groups with such a limited number of animals will be difficult. Therefore, it is proposed that treatment groups of 10 or fewer fish be exempted from the requirement to establish control groups. It is also proposed that species listed under the authority of the Endangered Species Act (ESA) be exempted from the requirement to establish control groups. With respect to species listed under the ESA, every fish may be critical to the restoration effort. In all other situations, investigators should make a serious effort to include a control group in the trial. Fish should be assigned to control or treatment groups randomly. Study fish should be crowded into a confined space where segregation and escape is impossible, and captured using dip nets. Fish in alternating nets should be assigned to control or treatment groups until desired fish numbers are obtained. Suggested control groups will be based on treatment population size according to the following schedule:

Treatment Group Size	Control Group Size[1]
0 - 10 fish	0 (too few fish for data analysis)
11 - 30 fish	5 fish
31 - 50 fish	10 fish
51 - 75 fish	15 fish
76 -100 fish	20 fish
101-300 fish	25 fish
>300 fish	30 fish

[1] Minimum number of fish per control group

C. 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.** Assignment to control and treatment groups should be random and designed to avoid bias. 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. Use of control groups will help to ensure that results of efficacy studies provide useful information that will support a NADA.

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

separate FDA-approved study protocol (i.e. not the INAD study protocol), and will also be conducted with assistance from, and under the direct supervision of, the sponsor. **If for any reason it becomes apparent to the sponsor that facilities/investigators listed under this INAD are not willing to participate in such "pivotal" studies, the sponsor will request that FDA terminate the INAD.**

XI. TREATMENT SCHEDULES

A. Route of administration

LHRHa Liquid/LHRHa is administered as either an intramuscular (IM) or intraperitoneal (IP) injection.

B. Dose to be administered

1. Injection

Standard priming dosage rate will be 20 ug $LHRH_a$/kg body weight and the standard resolving dose is 80 – 100 ug $LHRH_a$/kg. Although certain situations may require a higher priming dosage rate, dosage will never exceed 120 ug $LHRH_a$/kg body weight.

C. Dosing interval and repetition

Dependent upon the species/strain involved, LHRHa Liquid/LHRHa may be administered as a single treatment, or as a multiple treatment. Determination of whether single or multiple treatment regimens is used will be largely a matter of past experience of the investigator and literature citations reporting successful protocol with respect to specific species/strains. Multiple treatment regimens will generally consist of a single "priming" dose followed by a single "resolving" dose.

D. Drug preparation procedures

Powder formulation:

$LHRH_a$ for injection will be supplied in vials containing 1, 5, or 25 mg of a lyophilized white powder. Based on the relatively small amount of hormone per vial, investigators should not attempt to divide $LHRH_a$ into additional aliquots (unless a high quality analytical balance and a Good Laboratory Practice laboratory are available). Immediately prior to injection, $LHRH_a$ should be diluted using a sterile, physiological saline solution. Dilution volume is dependent upon dosage, size and number of fish to be injected, and desired injection volume.

Liquid Formulation:

LHRHa Liquid will be supplied in 100mL vials containing 80ug/mL of LHRHa in a liquid formulation. No dilution is required for this product.

E. Permissible concomitant therapy

Since efficacy data are being collected during the INAD process, there should be

no concomitant therapy. Preferably, there should be no other therapy during a period extending from 2 weeks prior to treatment to 2 weeks after treatment. Investigators must be prepared to make no changes in fish cultural procedures or environmental conditions, and apply no other hormone therapy once a decision has been made to conduct LHRHa Liquid/LHRHa treatment. However, if concomitant therapy is required in order to protect/propagate valuable fish stocks, AADAP should be contacted right away.

An exception to this concomitant therapy is that the MS222 and Aqui-S 20E anesthetics may be used to sedate fish prior to LHRHa treatment. If an anesthetic is used please note which one was used in Form LHRHa Liquid/LHRHa IIa-3 under the description of results section. Note: the withdrawal time must be followed for whichever anesthetic was used.

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 LHRHa Liquid/LHRHa - 3. Treatment response parameters that should be addressed include the following:

1. Primary Parameters

The primary response parameter for evaluating the effect of LHRHa Liquid/LHRHa on fish will be whether a fish is “ripe” or “non-ripe” following treatment. In the case of females, ripe fish are those that have released their eggs in response to normal artificial spawning procedures. In the case of males, ripe fish are those undergoing active spermiation. Non-ripe fish are the obvious converse. With respect to data reporting under this INAD, eggs will only be collected one time from individual fish.

2. Secondary Parameters

Secondary response parameters for females will include percent eye-up and percent hatch. Secondary response parameters for males will include the volume of milt (ml) available from individual fish and an evaluation of milt motility (percent motile spermatozoa). Motility evaluations will be reported using a scoring system that assigns each milt sample a motility score of either 0, 1, 2, 3 or 4. Motility scores will be based on the following schedule:

Percent Motility	Motility Score

0	0
1-25	1
26-50	2
51-75	3
76-100	4

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

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

3. Mortalities and Moribund Fish

Any fish that die or are euthanized during the study period should undergo a complete necropsy. Necropsy should include examination of the implant site. Necropsy results should be recorded in the Results Report –Form 3 in the Necropsy Report Data Entry table. If it appears that fish died due to handling stress that needs to be reported in the Results Report - Form 3.

XIII. FORMS FOR DATA COLLECTION

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

Form LHRHa Liquid/LHRHa-W. Worksheet for Designing Individual Field Trials under INAD 8061 - located in the New Study Request tab

Form LHRHa Liquid/LHRHa -1. Report on Receipt of Drug - Guide for Reporting Investigational

New Animal Drug Shipments for Poikilothermic Food Animals - located in the Manage/View Drug Inventory tab

Form LHRHa Liquid/LHRHa -2. Chemical Use Log for Clinical Field Trials Using LHRHa Liquid/LHRHa under INAD 8061 - located in the Manage/View Drug Inventory tab and filled out in Form LHRHa Liquid/LHRHa - 3 to show use

Form LHRHa Liquid/LHRHa -3. Results Report Form for use of LHRHa Liquid/LHRHa under INAD 8061 - located in the Active Studies table on the home page

Copies of these forms are attached to this Study Protocol and are to be used as a guide for collecting the data that will be entered into the online INAD database. **Actual reporting is accomplished on forms located on the online INAD database.**

XIV. RECORD KEEPING PROCEDURES

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

XV. DISPOSITION OF INVESTIGATIONAL ANIMALS

Fish may be released immediately following treatments. Edible tissues derived from experimental animals treated under this protocol may be marketed for human consumption or fish may be released into public waters for possible human consumption.

If Aqui-S 20E or MS222 are used when LHRHa Liquid/LHRHa treatments are in progress then **the longest of the withdrawal period is observed**.

XVI. DISPOSITION OF INVESTIGATIONAL DRUG

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

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

A. Drug distribution

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

B. Study Monitors

The Study Monitors are generally fish health professionals with experience in diagnosing and treating fish diseases, and the ability to monitor overall fish health with respect to ongoing fish culture practices. A study monitor will be selected by each facility that is authorized to treat fish with LHRHa Liquid/LHRHa. 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 LHRHa Liquid/LHRHa itself) are already available at each participating fish hatchery. In recent years, induced final gamete maturation has become a fairly common occurrence at many broodstock facilities. Fish hatchery managers (i.e., Investigators) are well trained and well equipped to handle these situations (see Appendix IIIb). If any additional equipment or materials are required, they will be provided by the Study Monitors (See Section VII.B. Items needed for sample collection, observations, etc.).

D. Administrator of the drug

LHRHa Liquid/LHRHa 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). LHRHa Liquid/LHRHa 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 protocol Section VII.A.6. Accountability for details and the following forms will be used as guides for data collection: Forms LHRHa Liquid/LHRHa-W, LHRHa Liquid/LHRHa -1, LHRHa Liquid/LHRHa -2, and LHRHa Liquid/LHRHa -3.

F. Recording observations

The Investigator or a person under his/her direct supervision will be responsible for implementing the Study Protocol, making observations, collecting samples, and recording data during the clinical field trials. After the data have been collected and

recorded on the forms, the Investigator will send the data to the Study Monitors who will ensure that all required information is provided. The Study Monitors will in turn send the data to the Study Director. The Study Director will analyze and summarize the data and prepare a 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, and must complete all required data forms (see Section XIII). The Investigator should forward all completed forms to the Study Monitor for review. Study Monitors should carefully check each set of data for accuracy and completeness. If a form is incomplete or inaccurate, it should be returned to the Investigator. If a form is complete and accurate, it should be forwarded to the Study Director at the AADAP Office. **Note:** data that is entered through the online INAD database will be archived in the database. These archived forms will be available as long as the study participant accounts remain open.

XVIII. PLANS FOR DATA ANALYSIS

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

XIX. PROTOCOL AND PROTOCOL AMENDMENTS

A signed copy of the Study Protocol must be retained by each Investigator. At any time before 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 contacted immediately. **Protocol deviations should be fully documented and should be accompanied by a written explanation of what happened, why, and what steps were taken to mitigate the deviation.** Deviation statements

should be documented on Form LHRHa Liquid/LHRHa-3 in the *Description of Results* section and in the *Study Deviation* field.

XXI: E.O. 13891

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

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Woods, L.C. and C.V. Sullivan. 1993. Reproduction of striped bass, (Morone saxatilis Walbaum), broodstock: monitoring maturation and hormonal induction of spawning. Aquaculture and Fisheries Management. 24:213-224.

Appendix I. Sponsor Contact Information for LHRHa Liquid/LHRHa INAD #8061

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

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

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

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

1

Appendix II. Study Monitors for LHRHa Liquid/LHRHa INAD #8061

Note: This information will be provided directly to CVM

1**Appendix IIIa. Facilities and Names of Investigators Participating under LHRHa Liquid/LHRHa INAD #8061**

Note: This information will be provided directly to CVM and Syndel

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

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

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

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

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

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

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

1

Appendix IV. Safety Data Sheet (SDS) for LHRHa Liquid/LHRHa INAD #8061

The SDS for LHRHa Liquid/LHRHa can be found at the drug sponsor's website:

The powder formulation SDS is located at:
https://syndel.com/wp-content/uploads/2021/09/LHRHa-SDS-16-Sep-2021.Rev_.pdf

The liquid formulation SDS is located at:
https://syndel.com/wp-content/uploads/2021/09/LHRHa-Liquid-SDS-Nov-19.Rev-Nov-19.pdf

1

Appendix V. Investigational Label for LHRHa Liquid/LHRHa INAD #8061

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

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

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

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

1

Appendix VIa. Fish Species Treated under LHRHa Liquid/LHRHa INAD #8061

All finfish

1

Appendix VIb. Table of Facilities and Fish Stocks Treated under LHRHa Liquid/LHRHa INAD #8061

Note: This information will be provided directly to CVM

All data must be entered through the online INAD database:

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

Form LHRHa Liquid/LHRHa-W: Worksheet for Designing IndividualField Trials Under LHRHa Liquid/LHRHa INAD 8061

INSTRUCTIONS

1. Investigator must fill out Form LHRHa Liquid/LHRHa-W for each proposed treatment under this INAD **before** actual use of LHRHa Liquid/LHRHa.
2. Investigator should forward a copy of LHRHa Liquid/LHRHa 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		Fax	

FISH CULTURE AND DRUG TREATMENT INFORMATION

Fish species to be treated						
Average fish size (in)					Average fish weight (gm)	
Number of treated males					Number of treated females	
Number of control males					Number of control females	
Anticipated date treatment will be initiated					Estimated total amount of drug for proposed treatments (mg)	
Intended LHRHa Liquid/LHRHa dosage (ug/kg)		Female		Male	Method of administration (IP or IM Injection)	
Number of injections		Female		Male	Injection interval (hrs or days)	
Drug manufacturer					Drug lot (powder) or batch (liquid) number	
Which LHRHa formulation will you be using (powder or liquid)?						

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

Study designed by _____

DISPOSITION OF TREATED FISH (Human Food Safety Considerations):

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

☐ Investigator should 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:

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

Date Prepared: _____ **Investigator:** _____

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

FORM LHRHa Liquid/LHRHa-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 LHRHa Liquid/LHRHa-1 **immediately** upon receipt of LHRHa Liquid/LHRHa.
2. Investigator should forward a copy of Form LHRHa Liquid/LHRHa -1 to the Study Director at the AADAP Office

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

Name of Drug	**LHRHa Liquid/LHRHa**	INAD Number	**8061**
Proposed Use of Drug	To induce gamete maturation in a variety of fish species.		
Date of CVM Authorization Letter	07/15/2020		
Date of Drug Receipt		**Amount of Drug Received**	
Drug Lot/Batch Number		**Study Worksheet Number**	
Name of Investigator			
Address of Investigator			
Location of Trial			
Pivotal Study (yes/no)		Non-pivotal Study (yes/no)	
Approximate Number of Treated Animals		**Approximate Number of Control Animals**	
Number of Animals Used Previously[1]			
Study Protocol Number	8061		
Approximate dates of trial (start/end)			
Species, Size, and Type of Animals			
Maximum daily dose and duration	120 ug/Kg body weight		
Methods of Administration	IP or IM Injection		
Withdrawal Period	Zero days; follow MS222 or Aqui-S 20E withdrawal time if it is used to sedate fish at time of injection		

[1] **To be filled out by the AADAP Office**

Date Prepared: _____ **Investigator:** _____

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

Date Reviewed: _____ **Sponsor:** _____

Form LHRHa Liquid/LHRHa-2: Chemical Use Log for Clinical Field Trials Using LHRHa Liquid/LHRHa Under INAD 8061

Instructions:

1. Initiate Form LHRHa Liquid/LHRHa-2 **immediately** upon receipt of LHRHa Liquid/LHRHa.
2. Each lot number of LHRHa Liquid/LHRHa may be used for multiple treatment regimens.

Qty of LHRHa Liquid/LHRHa from Reporting

Previous page (mg)_____Facility_____Individual_____

Date	Amount of new LHRHa Liquid/ LHRHa received (mg)	Lot/Batch number of LHRHa Liquid/ LHRHa received	Study Number	Amount of LHRHa Liquid/ LHRHa used in treatment (mg)	LHRHa Liquid/ LHRHa transferred (mg)	LHRHa Liquid/ LHRHa discarded (mg)	LHRHa Liquid/ LHRHa remaining on hand (mg)	Inventory by (Initials)
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						
	xxxx	xxxx						

Date Prepared: _____ **Investigator:** _____

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

STUDY Number _____

Form LHRHa Liquid/LHRHa-3: Results Report Form for Clinical Field Trials Using LHRHa Liquid/LHRHa Under INAD 8061

INSTRUCTIONS

1. Investigator must fill out Form LHRHa Liquid/LHRHa-3 no later than **10 days** after completion of treatment. Attach lab reports and other pertinent study information.
2. If LHRHa Liquid/LHRHa 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 LHRHa Liquid/LHRHa-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

Drug lot number		Total amount drug used (mg)	
Fish species treated		Water temperature (^{o}F)	
Drug dosage male (ug/kg body wt)		Drug dosage female (ug/kg body wt)	
Average fish weight (gm)		Average fish length (in)	
Number of treated males		Number of treated females	
Number of control males		Number of control females	
LHRHa Formula used (liquid or powder)		Treatment dates	
Treatment method (IP or IM injection)		Injection interval (hrs or days)	
Number of injections/males		Number of injections/females	
Spawning/evaluation interval (time from treatment until spawning)		Spawning/evaluation date	

Hormone Results Record - Version 4

INSTRUCTIONS

1. "Ripe" females are those fish that have ovulated or released their eggs; "ripe" males are those fish that are actively spermiating. "Non-ripe" fish are the converse after treatment.
2. Motility Score based on a scale of 0 - 4 (see Study Protocol Section XII).
3. Use additional copies of this form for additional treatment days.

Be sure the facility name is written here: _____

		TREATED FISH - Females						**CONTROL FISH - Females**					
Date Treated	Date Evaluated	# of Fish	# Ripe	# Non-Ripe	% Ripe	% Eye-Up	% Hatch	# of Fish	# Ripe	# Non-Ripe	% Ripe	% Eye-up	% Hatch

		TREATED FISH - Males						**CONTROL FISH - Males**					
Date Treated	Date Evaluated	# of Fish	# Ripe	# Non-Ripe	% Ripe	Milt/ fish (mL)	Motility Score	# of Fish	# Ripe	# Non-Ripe	% Ripe	Milt/ fish (mL)	Motility Score

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

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

OBSERVED WITHDRAWAL PERIOD OF TREATED FISH:

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

☐ **NEGATIVE REPORT** Luteinizing Hormone-Releasing Hormone Analog was not used at this facility under this Study Number during the reporting period. The study will be closed out in the online INAD database.

Date Prepared: _____ **Investigator:** _____

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

NOTICES

Paperwork Reduction Act

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

ESTIMATED BURDEN STATEMENT

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

FREEDOM OF INFORMATION ACT STATEMENT

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