

**STUDY PROTOCOL FOR A COMPASSIONATE AQUACULTURE
INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR
COMMON CARP PITUITARY (CCP) INAD 8391**

Sponsor:

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

Sponsor Signature

Date Approved

Manufacturer/Source of Supply:

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8547 152nd Ave NE
Redmond, WA 98052

Office for Coordination of CCP INAD:

Aquatic Animal Drug Approval Partnership
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Bozeman, Mt 59715

Proposed Starting Date: January 1, 2021

Proposed Ending Date: December, 2026

Study Director: Bonnie Johnson

Clinical Field Trial Location:

Facility: _____

Investigator: _____

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STUDY PROTOCOL FOR A COMPASSIONATE AQUACULTURE INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR COMMON CARP PITUITARY (CCP) UNDER INAD #8391

I. STUDY IDENTIFICATION AND TITLE

Clinical field trials to determine the efficacy of common carp pituitary (CCP) to induce gamete maturation (ovulation and spermiation) in a variety of fish species.

II. SPONSOR

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

III. INVESTIGATORS/FACILITIES

See Appendix IIIa for names and addresses.

IV. PROPOSED STARTING AND COMPLETION DATES:

Proposed Starting Date: January 1, 2021

Proposed Completion Date: December, 2026

V. BACKGROUND/PURPOSE

A. Background Information:

The use of hormones to induce spawning in fish is critical to the success of many fisheries programs in the United States. 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 in fish can be induced by the administration of a variety of hormones (Donaldson and Hunter 1983; Goetz 1983). The first reported studies investigating the hormonal control of reproduction in fish utilized intraperitoneal injection of freshly dissected pituitary glands (Houssay, 1931; von Ihering, 1937). The use of CCP was first reported in the United States by Hasler et al., (1939, 1940). These and many other early studies investigating the use of fish pituitaries to induce gamete maturation in a variety of fish species were thoroughly reviewed by Pickford and Atz (1957) in their comprehensive treatise on the fish pituitary gland.

The efficacy of CCP to induce ovulation and spermiation in fish is well documented (Chaudhuri, 1976). CCP has been shown to induce gamete maturation in a wide variety of species including; common carp, grass carp, silver carp, bighead carp, striped bass, white bass, goldfish, lake sturgeon, white sturgeon, channel catfish, flathead catfish, mullet, muskellunge, bigmouth buffalo, lake trout, brook trout, walleye, yellow perch, northern pike, and white crappie to name a few. Not only was carp pituitary injection one of the very first methods of inducing ovulation and spermiation in fish, it has stood the test of time and is still the preferred methodology of many fish culturists.

Currently, the use of CCP is an important management/production tool in the propagation of a number of important species. In some situations, it has been found to be the most efficient and reliable method of inducing final gamete maturation. The success many commercial aquaculture production programs, as well as a considerable number of

supplementation/recovery/restoration programs, are dependent upon its continued availability for use as an aid in spawning fish.

B. Purpose of INAD:

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

USFWS anticipates requesting that FDA grant an extension of the CCP INAD for additional years at the end of this treatment season. The USFWS is aware that opportunities for CCP 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 CCP 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 CCP on gamete maturation in both cultured fish under typical hatchery situations and on critical wildstock species.
2. Provide the opportunity for fish culturists and fisheries managers to legally use CCP 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 a NADA on CCP in fish. Specifically, CCP 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

Common Name: Common Carp Pituitary

Appearance: Brownish/White powder

Odor: None

b. Strength and dosage form

CCP is obtained by dissection as a fresh material from adult common carp (*Cyprinus carpio*). Whole pituitaries are desiccated using an alcohol/acetone rinse, ground into a powder, and stored. CCP is prepared for injection by suspending the powder in sterile water or physiological saline.

c. Manufacturer, source of supply

Argent Aquaculture
8547 152nd Ave NE
Redmond, WA 98052

Contact Person: Thomas Sawtell
Phone: 425-605-0933
email: sales@argentaquaculture.com
Website: <http://argentaquaculture.com/>

2. Verification of Drug Integrity/Strength:

The Manufacturer will provide the analytical data necessary to establish the purity of each lot of CCP supplied. The lot number and date of processing for each batch of CCP 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 CCP-1) will clearly identify the lot number for all CCP shipments. If the integrity of the CCP 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 CCP-2). All un-usable CCP must be destroyed by following the disposal methods described in the MSDS.

3. Storage Conditions

CCP will be stored in the original container supplied by the Manufacturer with the appropriate investigational label attached. The container will be stored in a cool, dry location. If CCP is stored in a refrigerator, 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*". CCP 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 CCP (see Appendix IV). Each person involved with the study and each person who may be present during the use of CCP shall be required to read the SDS. Safety precautions as outlined in the SDS will be followed at all times when working with CCP.

5. Investigational Labeling

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

6. Accountability

Argent Aquaculture will be the sole supplier of CCP to all Investigators under this INAD.

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. Immediately upon receiving an order/shipment of CCP, the Investigator will complete Form CCP-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 in turn forward a copy to FDA. Arrangements should be made between Investigators and Study Monitors to ensure completed Form CCP-1s are received by the Study Director within 10 days of drug receipt.

All Investigators are also responsible for maintaining an accurate inventory of CCP on-hand. A Chemical Use Log (Form CCP-2) must be completed and maintained by each Investigator. Each time CCP 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 CCP will be disposed of by following the disposal methods in the Safety Data Sheet (note: unless CCP is planned for use in another approved field trial, and planned usage is within the storage guidelines established by the manufacturer). Disposition of all CCP must be properly recorded and accounted for in the Drug Inventory Form of the database which is Form CCP-2. The Study Monitor will be responsible for verifying the quantity of CCP remaining on hand versus the amount indicated on Form CCP-2. **Note:** CCP can be transferred to other facilities that are participating under INAD 8391. Transfers must be shown in the Drug Inventory section of the database (formerly Form CCP -2).

7. Preparation Procedures

CCP for injection will be supplied in vials containing 1 - 25 g of desiccated powder. CCP is prepared for injection by suspending the powder in sterile water or physiological saline. The amount of CCP needed for each treatment will be weighed on an accurate laboratory scale, preferably to the nearest milligram. Dilution volume is dependent upon dosage, size and number of fish to be injected, and desired injection volume.

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 CCP INAD will need to complete several forms 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 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, it is strongly encouraged that whenever possible, the experimental unit in clinical field trials is individual animals. Whenever 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 CCP can be ordered and dispensed under this INAD. Last minute deviations can be requested by the Sponsor or by an Investigator to address emergency-use situations (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

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

D. Environmental conditions

Since CCP activity is rapidly lost in dilute aqueous solution, there will be no drug discharge from participating facilities. Therefore, CCP qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.33(e).

Environmental conditions will be variable and include a spectrum of water temperatures and water quality parameters. Environmental conditions will be reported on Form CCP-3.

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 CCP-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 CCP-2 and CCP-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

CCP treatment. In some cases, particularly with respect to wildstock populations, the number of broodfish available at a given time for CCP 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 would 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:

<u>Treatment Group Size</u>	<u>Control Group Size¹</u>
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

¹Minimum 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**

CCP. 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

CCP should be dissolved in sterile physiological saline or sterile water and administered as either an intraperitoneal (IP) or intramuscular (IM) injection.

B. Dose to be administered

Standard dosage rates will be 4-10 mg CCP/kg body weight. Although certain situations may require a higher dosage rate, dosage will never exceed 25 mg CCP/kg body weight.

C. Dosing interval and repetition

Dependent upon the species/strain involved, CCP may be administered as a single treatment, or as a multiple treatment. Determination of whether single or multiple treatment regimen 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 regimen will generally consist of a single "priming" dose followed by a single "resolving" dose.

D. Drug preparation procedures

CCP will be supplied by Argent Aquaculture in vials containing 1- 25 g of a desiccated brownish/white powder. CCP is prepared for injection by suspending the powder in sterile water or physiological saline. The amount of CCP needed for each treatment will be weighed on an accurate laboratory scale, preferably to the nearest milligram. Dilution volume is dependent upon dosage, size and number of fish to be injected, and desired injection volume.

E. 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 hormone therapy once a decision has been made to conduct CCP treatment. However,

if concomitant therapy is required in order to protect/propagate valuable fish stocks, AADAP should be contacted right away.

XII. TREATMENT RESPONSE PARAMETERS

The collection and reporting of source data begin 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 CCP-3. Treatment response parameters that should be addressed include the following:

1) Primary Parameters

The primary response parameter for evaluating the effect of CCP 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 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 apparent level of stress, negative fish behavior, etc.

3) Adverse Reactions

Any adverse reaction that occurs during the study period (whether considered/suspected to be treatment-related or not) 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 CCP has been used 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.

4) 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 CCP INAD will need to complete the following forms:

Form CCP-W. Worksheet for Designing Clinical Field Trials under INAD 8391

Form CCP-1. Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals

Form CCP-2. Drug Inventory Form for use of CCP under INAD 8391

Form CCP-3. Results Report Form for use of CCP under INAD 8391

Form CCP-4N. Necropsy Report

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.

XVI. DISPOSITION OF INVESTIGATIONAL DRUG

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

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

A. Drug distribution

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

B. Study Monitors

Study Monitors are generally fish health professionals with experience in diagnosing and treating fish diseases, and the ability to monitor overall fish health with respect to ongoing fish culture practices. A study monitor will be selected by each facility that is authorized to treat fish with CCP. 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 CCP 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

CCP 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). CCP 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 CCP-W, CCP-1, CCP-2, CCP-3, and CCP-4N.

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 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 forwarded to FDA for review. Copies of the signed amendment will be attached to each copy of the Study Protocol. **Investigators will be liable for non-compliance violation if drugs are used without a Study Protocol or in a manner different than specified in the Study Protocol, if forms are not filed on time, or if the study data are not properly collected, maintained, and reported.** The Study Monitor is responsible for ensuring that all INAD procedures are being followed as defined by the Study Protocol.

XX. PROTOCOL DEVIATIONS

Deviations from the established Study Protocol occasionally cannot be avoided. If deviations occur, the Study Monitor should be notified immediately. **Protocol deviations should be fully documented and should be accompanied by a written explanation of what happened, why, and what steps were taken to mitigate the deviation.** Deviation statements should be documented on Form CCP-3 in the *Description of Results* section and in the *Study Deviation* field.

XXI: E.O. 13891

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

LITERATURE CITED

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Appendix I. Sponsor Contact Information for CCP INAD #8391

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

Appendix II. Study Monitors for CCP INAD #8391

Note: This information will be provided directly to CVM

Appendix IIIa. Facilities and Names of Investigators Participating under CCP INAD #8391

Note: This information will be provided directly to CVM and Argent Aquaculture

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

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

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

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

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

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

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

Appendix IV. Safety Data Sheet (SDS) for CCP INAD #8391

SAFETY DATA SHEET

SECTION 1: Identification

1.1 Product Name

Product Name: **Common Carp Pituitary Extract (Acetone Dried Powder)**

Product Item Number: C-CARP-CCP

Brand: Argent Aquaculture

1.2 Product uses

Specific use: USFWS INAD 8391

1.3 Company name:

Argent Aquaculture LLC

8547 152nd Ave. NE

Redmond, WA 98052

United State of America

Telephone: 425-606-0933

Fax: 425-605-4505

1.4 Emergency telephone number

Emergency Telephone No: 425-605-0933

SECTION 2: Harzard Identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture.

2.2 GHS Label elements, including precautionary statements

Not a hazardous substance or mixture.

2.3 Hazards not otherwise classified (HNOC) or not covered by GHS.

None.

SECTION 3: Composition / Information on Ingredients

3.1 Substances

No components need to be disclosed according to the applicable regulations.

SECTION 4: First-Aid Measures

4.1 Description of first-aid measures

If inhaled

Move person to fresh air. If not breathing, give artificial respiration.
mouth to an unconscious person. Rinse mouth with water.

In case of contact with skin

Wash with soap and lots of water.

In case of eye contact

Flush eyes with water as precaution.

If swallowed

Never give anything by mouth to an unconscious person. Use water to rinse mouth.

4.2 Most important symptoms and effects, acute and delayed.

The most important known symptoms and effects are described in Section 2.2 and section 11.

4.3 Indication of any immediate medical attention and special treatment needed.

No data available.

SECTION 5: Fire-Fighting Measures

5.1 Extinguishing media

Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

5.2 Special hazards arising from the substance or mixture.

Nature of decomposition products is not known.

5.3 Advise for firefighters

Wear self-contained breathing apparatus of firefighting if necessary.

5.4 Further Information.

No data available.

SECTION 6: Accidental Release Measures

6.1 Personal precaution, protective equipment and emergency procedures

Avoid dust formation. Avoid breathing product powder particles, vapors, mist or gas.
For personal protection see Section 8.

6.2 Environmental precautions

Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up

Sweep up and collect residual with damp disposable paper towel. Keep in suitable, closed containers for disposal.

6.4 Reference to other sections

For disposal refer to Section 13.

SECTION 7: Handling and Storage

7.1 Precautions for safe handling

Provide appropriate exhaust ventilation at places where any product powder / dust may be formed.

7.2 Conditions for safe storage, including any incompatibilities

Keep container tightly closed in a dry and well-ventilated place.
Recommended long term storage refrigerate or freeze -20 deg.C .
Storage Class (TRGS 510) Non Combustible Solid.

7.3 Specific end use.

See Section 1.2.

SECTION 8: Exposure Controls / Personal Protection

8.1 Control parameters

Components with workplace control parameters

Contains no substances with occupational exposure limit values.

8.2 Exposure controls

Appropriate engineering controls

Follow general industrial hygiene practices.

Personal protective equipment.

Eye and face protection

Use proper equipment for eye protection as tested and approved under government standards (NIOSH (US) or EN 166(EU).

Skin protection

Handle product with gloves. Inspect gloves for integrity before use. Follow safe removal technique to take off gloves and avoid skin contact with contaminated glove surfaces. Dispose of gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

Body Protection

Select and wear body protection in relation to its type, and to the concentration, and amount of any associated dangerous substances or equipment, and to the specific workplace. The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

Respiratory protection

Respiratory protection is not required but recommended when product powder is handled. Use type N95 (US) or type P1 (EN 143) dust masks. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Control of environmental exposure

Do not let product enter drains.

SECTION 9: Physical and Chemical Properties

9.1 Information on basic physical and chemical properties

Appearance	White tan powder
Odor	No Data Available
Odor Threshold	No Data Available
pH	No Data Available
Melting point	Decomposes
Freezing point	No Data Available
Initial boiling point and boiling range	No Data Available
Flash point	No Data Available
Evaporation rate	No Data Available
Flammability	No Data Available
Upper / lower flammability or explosive limits	No Data Available
Vapor pressure	No Data Available
Vapor density	No Data Available
Relative density	No Data Available
Water solubility	No Data Available
Partition coefficient n-octanol / water	No Data Available
Autoignition temp.	No Data Available
Decomposition temp.	No Data Available
Viscosity	No Data Available
Explosive properties	No Data Available
Oxidizing properties	No Data Available

SECTION 10: Stability and Reactivity

10.1 Reactivity

No data available.

10.2 Chemical stability

Stable under recommended storage conditions and identified uses.

10.3 Possibility of hazardous reaction

No data available.

10.4 Conditions to avoid

Store dry do not expose to moisture before use.

10.5 Incompatible materials

No data available.

10.6 Hazardous decomposition products

No data available.

In case of fire see Section 5.

SECTION 11: Toxicological Information

Information on toxicological effects

Acute toxicity

Inhalation: No data available.

Dermal: No data available.

Skin corrosion and irritation

No data available.

Serious eye damage and eye irritation

No data available.

Respiratory or skin sensitization

No data available.

Carcinogenicity

IARC: No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

ACGIH!: No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by ACGIH.

NTP: No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.

OSHA: No component of this product present at levels greater than or equal to 0.1% is on OSHA's list of regulated carcinogens.

Reproductive toxicity

No data available.

Specific target organ toxicity – Single exposure

No data available.

Specific target organ toxicity – Repeated exposure

No data available.

Aspiration hazard

No data available.

Additional information

RTECS: Not available.

SECTION 12: Ecological Information

Toxicity

No data available.

Persistence and degradability

No data available.

Bio-accumulative potential

No data available.

Mobility in soil

No data available.

Results of PBT and vPvB assessment

PBT / PvB assessment is not available as chemical safety assessment is not required.

Other adverse effects

No data available.

SECTION 13: Disposal Considerations

Waste treatment methods

Product

Unused, in accordance with Section 1.2; or regulatory approved disposal process.

Contaminated packaging

Regulatory approved disposal process.

SECTION 14: Transport Information

DOT USA

Not dangerous goods.

IMDG

Not dangerous goods.

IATA

Not dangerous goods.

SECTION 15: Regulatory Information

SARA 302 Components

No chemicals in this product are subject to the reporting requirements of SARA Title III Section 302.

SARA 311/312 Hazards

No SARA Hazards.

SARA 313 Components

This product does not contain any chemical components with known CAS numbers that exceed the threshold reporting levels established by SARA Title III Section 313.

Massachusetts Right To Know Components

No components are subject to the Massachusetts Right To Know Act.

Pennsylvania Right To Know Components

Common Carp Pituitary Extract (Acetone Dried Powder).

New Jersey Right To Know Components

Common Carp Pituitary Extract (Acetone Dried Powder).

California Proposition 65 Components

This product does not contain any chemicals known to State of California to cause cancer, birth defects, or any other reproductive harm.

SECTION 16: Other Information

Argent Aquaculture LLC. SDS intended for use by Facilities and Investigators under INAD 8391.

The information in this SDS is considered current and reliable, but is not all inclusive and shall be used only as a guide. We encourage users to conduct their own testing best suited for their purposes under their conditions. This SDS does not represent a guarantee of the content or properties of the product. The data is provided without any warranty, expressed or implied, regarding its correctness or accuracy. Since the conditions for use, handling, storage and disposal are beyond Argent Aquaculture's control, it is the responsibility of the user to determine safe conditions for use and to assume liability for loss, damage, or expenses arising from improper use. No warranty expressed or implied regarding the product described herein will be created by or inferred from any statement or omission. Argent Aquaculture shall not be held liable for any damage resulting from handling, contact or use of the product. Various agencies may have specific regulations concerning the transportation, handling, storage, use or disposal of this product which may not be reflected in the SDS. The user should review these regulations to ensure full compliance.

Created: January 16, 2014 Last Updated: May 22, 2020

Appendix V. Investigational Label for CCP INAD #8391

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."

Appendix VIa. Fish Species Treated under CCP INAD #8391

All finfish

Appendix VIb. Table of Facilities and Fish Stocks Treated under CCP INAD #8391

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 CCP-W: Worksheet for Designing Clinical Field Trials under CCP INAD 8391

INSTRUCTIONS

1. Investigator must fill out Form CCP-W for each trial conducted under this INAD **before** actual use of CCP.
2. Investigator should forward a copy of CCP-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 of treatment				Estimated total amount of drug for proposed treatments (mg)		
Intended CCP dosage (mg/kg)		Female		Male	Method of administration (IP or IM injection)	
Number of injections per fish		Female		Male	Injection interval (hrs)	
Drug manufacturer	Argent Aquaculture			Drug lot number		

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) 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 Material Safety Data Sheet for Common Carp Pituitary and have been provided protective equipment, in good working condition, as described in the SDS.

Date Prepared: _____

Investigator: _____

Date Reviewed: _____

Study Monitor: _____

FORM CCP-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 CCP-1 **immediately** upon receipt of CCP.
2. Investigator should forward a copy of Form CCP-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	CCP	INAD Number	8391
Proposed Use of Drug	To induce gamete maturation in a variety of fish species.		
Date of CVM Authorization Letter	March 6, 2020		
Source of Drug	Argent Aquaculture		
Date of Drug Receipt		Amount of Drug Received	
Drug Lot Number		Study Worksheet Number	
Name of Investigator			
Address of Investigator			
Location of Trial			
Approximate Number of Treated Animals			
Study Protocol Number	8391		
Approximate dates of trial (start/end)			
Species, Size, and Type of Animals			
Maximum total dose	25 mg/Kg body weight		
Methods of Administration	IP or IM Injection		
Withdrawal Period	Zero days		

Date Prepared: _____

Investigator: _____

Date Reviewed: _____

Study Monitor: _____

Date Reviewed: _____

Sponsor: _____

Form CCP-2: Drug Inventory Form
For Use in CCP Clinical Field Trials Conducted under CCP INAD 8391

INSTRUCTIONS

1. Investigator should initiate a new form CCP-2 **immediately** upon receipt of each shipment of Common Carp Pituitary.
2. Each lot number of CCP may be used for multiple treatment regimes.

Qty of CCP from _____ Facility _____ Reporting individual _____
 previous page (mg) _____

Date	Amount of new CCP received (mg)	Lot number of CCP received	Study Number	Amount of CCP used in treatment (mg)	CCP transferred (mg)	CCP discarded (mg)	CCP 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						
	XXXX	XXXX						
	XXXX	XXXX						
	XXXX	XXXX						
	XXXX	XXXX						
	XXXX	XXXX						

Date Prepared: _____

Investigator: _____

Date Reviewed: _____

Study Monitor: _____

Form CCP-3: Results Report Form
For Use in CCP Clinical Field Trials conducted under CCP INAD 8391

INSTRUCTIONS

1. Investigator must fill out Form CCP-3 no later than **10 days** after completion of the study period. Attach lab reports and other information.
2. If CCP 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 CCP-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 (°F)	
Drug dosage male (mg/kg body wt)		Drug dosage female (mg/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	
Treatment dates			
Number of injections per males		Number of injections per females	
Injection interval (hrs)		Method of administration (IP or IM injection)	
Spawning/evaluation interval (time from treatment until spawning)		Spawning/evaluation date	

Hormone Results Record

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	Number Ripe	Number Green	% Ripe	% Eye-Up	% Hatch	# of Fish	Number Ripe	Number Green	% Ripe	% Eye-Up	% Hatch

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

_____ Number of days before human consumption. Ensure this time period meets the withdrawal period described in Section XV of the Study Protocol.

_____ **NEGATIVE REPORT** CCP 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: _____

Form CCP-4N: Necropsy Report Form
For Use in CCP Clinical Field Trials conducted under CCP INAD 8391

INSTRUCTIONS

1. Investigator must fill out Form CCP-4N for all fish that die or are euthanized during the study period. Use a new copy of Form CCP-4N for each individual fish.
2. This information will be reported in the Necropsy Report Data Entry table located in the Results Report Form in the online database.

Date _____ Fish Species/ID _____ Fish Length (cm) _____

Evaluator(s): _____

Body surface: ___ normal ___ excess mucus ___ irregular color ___ other _____

Dermal lesion: ___ none ___ hemorrhagic ___ other _____

___ closed ___ open

Location: ___ dorsal ___ caudal ___ ventral ___ lateral ___ cranial

___ base of fin - Pectoral (right), Pectoral (left), Adipose, Dorsal, Anal, or Caudal

Gills: ___ normal ___ pale ___ hemorrhagic ___ other _____

Liver: ___ normal ___ pale ___ mottled ___ other _____

Spleen: ___ normal ___ pale ___ enlarged ___ other _____

Kidney: ___ normal ___ pale ___ swollen ___ other _____

Notes and comments of gross pathologies on other organs and tissues.

eyes _____

stomach _____

body cavity _____

gastrointestinal tract _____

gall bladder _____

gas bladder _____

adipose tissue _____

musculature _____

implant site _____

other _____

Investigator: _____ Date: _____