

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

**Sponsor:**

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

*David Edwards*

Sponsor Signature FOR

*Gary Edwards*

4/22/96

Date Approved

**Manufacturer/Supplier:**

Stoller Fisheries  
1301 18th Street  
P.O. Box B  
Spirit Lake, Iowa 51360

Argent Chemical Company  
8702 152nd Avenue, N.E.  
Redmond, Washington 98052

**Facility for Coordination of CCP INAD:**

Bozeman National INAD Office  
4050 Bridger Canyon Road  
Bozeman, Mt 59715

Proposed Starting Date

January 1, 1996

Proposed Ending Date

December 31, 1996

Study Director

Dr. David Erdahl

*David Erdahl*

Study Director Signature

4/22/96

Date

**Clinical Field Trial Location and Trial Number:**

\_\_\_\_\_  
Type or Print Facility Name

\_\_\_\_\_  
Trial Number

Investigator \_\_\_\_\_

\_\_\_\_\_  
Type or Print Name

\_\_\_\_\_  
Investigator Signature

\_\_\_\_\_  
Date

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

**I. STUDY ID AND TITLE**

Clinical field trials to determine the efficacy of CCP to induce gamete maturation (ovulation and spermiation) in a variety of fish species. INAD #8391.

**II. SPONSOR**

Gary B. Edwards, Assistant Director, Fisheries, U.S. Fish and Wildlife Service, 1849 C Street, N.W., Arlington Square Building, Mail Stop 725, Washington, D.C. 20240. Telephone: 703/358-1710; FAX: 703/358-2228.

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**Study Director:** Dr. David Erdahl, Bozeman National INAD Office, 4050 Bridger Canyon Road, Bozeman, Montana, 59715. Telephone: (406) 587-9265 extension 125; FAX: (406) 582-0242

**Principal Regional INAD Coordinators:** See Appendix I for names and addresses.

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

**III. INVESTIGATORS/FACILITIES**

See Appendix IIIa for names and addresses. Each facility has been assigned a trial number that reflects the INAD number (8391) and a unique number for that facility (e.g., Dexter NFH & TC #8391-19).

#### IV. PROPOSED STARTING AND COMPLETION DATES:

Proposed Starting Date: January 1, 1996

Proposed Completion Date: December 31, 1996

#### 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 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. On a world-wide basis, CCP is the most widely used material to induce final gamete maturation (spawning) in fish.

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.

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 regimes 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 CCP, or for declaration by U.S. Food and Drug Administration (FDA) that CCP is a low regulatory priority substance.

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 USFWS fish culturists 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 an 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

Stoller Fisheries  
1301 18th Street  
P.O. Box B  
Spirit Lake, Iowa 51360  
Phone: (712) 336-1750

Argent Chemical Company  
8702 152nd Avenue, N.E.  
Redmond, Washington 98052  
Phone: (800) 426-6258

#### 2. Verification of drug integrity/strength:

The Manufacturer/Suppliers will provide the documentation necessary to establish 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 "Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals" (Form 1) will clearly identify the lot number and date of processing of 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 2). The Study Monitor assigned to the Investigator involved will be immediately notified.

### 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 Material Safety Data Sheet (MSDS) for CCP (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 MSDS. Safety precautions as outlined in the MSDS will be followed at all times when working with CCP.

### 5. Investigational labeling

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

### 6. Accountability

Each USFWS Investigator will notify FDA prior to any shipment of CCP for use under this INAD. Immediately upon placing an order with the approved supplier, the Investigator will complete Form 1, "Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals" and send it to his/her Study Monitor. The Study Monitor will then send the original plus two copies to the FDA. Both the Investigator and the Study Monitor are required to sign Form 1. The Study Monitor will also send a single copy of Form 1 to the Study Director at the Bozeman National INAD Office. The Investigator will keep one copy of the completed Form 1 for the facility's INAD file. Arrangements should be made between Investigators and Study Monitors to insure completed Form 1s are received by the FDA within 7 days of the date an order was placed.

Investigators are also responsible for maintaining an accurate inventory of CCP on-hand. A Chemical Use Log (Form 2) will be supplied to each Investigator. Each time CCP is used, it must be reported by the Investigator on Form 2.

### 7. Preparation Procedures

CCP for injection will be supplied in vials containing 1- 25 g of a dessicated 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. These forms are described in Section XIII (p 10). Copies of these forms are attached to this Study Protocol.

### 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 before CCP can be ordered and dispensed under this INAD. Last minute deviations can be requested by the Sponsor, by an Investigator, or by a Study Monitor to control emergency disease outbreaks (See Section XX).

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 25.24(d)(4).

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).

## X. TREATMENT GROUPS

A. A treatment group or experimental unit may be an entire tank, pond, raceway, or group of fish, or it may be individual animals.

B. 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 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:

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<u>Treatment Group Size</u>	<u>Control Group Size<sup>1</sup></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

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<sup>1</sup> Minimum number of fish per control group

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 ensure that results of efficacy studies provide useful information that will support a NADA.

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

## **XI. TREATMENT SCHEDULES**

### **A. Route of administration**

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 regime 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 regime will generally consist of a single "priming" dose followed by a single "resolving" dose.

### **D. Drug preparation procedures**

CCP for injection will be supplied 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, it should be fully documented and the efficacy data from the CCP treatment involved should be appropriately labeled.

## XII. TREATMENT RESPONSE PARAMETERS

The collection and reporting of source data begins with the decision to treat valuable fish based on hatchery records or other pertinent species information indicating treatment is warranted. Daily morbidity and mortality records, case history records, as well as any extenuating or mitigating circumstances that may affect treatment response need to be documented. All pertinent treatment response parameters should be reported on Form 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 percent of fish ripe following treatment. In the case of females, ripe fish are those that have ovulated. In the case of males, ripe fish are those undergoing active spermiation.

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 CCP has been used extensively with beneficial effect in fish culture for over 50 years, it is possible adverse reactions may occur under certain environmental conditions or with respect to specific species/strains of fish. Carefully observe all treated fish for any signs of any adverse reaction to treatment. The Investigator should carefully document all observations of adverse reactions. If any signs of drug toxicity are detected, they should also be documented and immediately reported to the Study Monitor, who will in turn notify the Study Director.

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

## XIII. FORMS FOR DATA COLLECTION

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

- Form 1. Guide for reporting investigational new animal drug shipments for poikilothermal food animals.
- Form 2. Chemical use log for clinical field trials using CCP under INAD #8391.
- Form 3. Diagnosis, treatment, and response record for clinical field trials using CCP under INAD #8391.
- Form 4. Disposal record for animals from clinical field trials using CCP under INAD #8391.

Copies of these forms are attached to this Study Protocol.

#### **XIV. RECORD KEEPING PROCEDURES**

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

#### **XV. DISPOSITION OF INVESTIGATIONAL ANIMALS**

Animals that die during treatment should be disposed of by burial or incineration. All treated fish will be maintained in culture facilities or captivity for at least 72 hours following treatment before they are released or allowed to enter the food chain. Injected domestic (non-wild) broodstock will be maintained in culture facilities for at least 30 days following CCP treatment. If fish are injected more than once, these requirements will be based on the time of final treatment.

No withdrawal period will be required for injected fish that will be illegal for harvest for 30 or more days after release. No withdrawal period shall be required for dead fish that will be buried or rendered into non-edible products.

In some cases, treated fish may be sacrificed for investigational purposes. The Investigator must record the disposition of all treated fish on Form 4.

#### **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. The investigational drug may not be redistributed to others not specified by the protocol and may not be retained by the Investigator after completion of the study.

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

### **A. Drug distribution**

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

### **B. Study Monitors**

The Study Monitors are generally fish health professionals with experience in diagnosing and treating fish diseases. There is one Study Monitor assigned to each facility within the USFWS that is covered by the CCP INAD. A list of Study Monitors, along with addresses and phone numbers, can be found in Appendix II. The Study Monitors are responsible for supervision of the trials, adherence of 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., page 6).

### **D. Administrator of the drug**

CCP will be administered directly by the assigned Investigator (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 Section VII.A.6. Accountability (page 5) for details and Forms 1-4 for actual forms to be used in the study.

### **F. Recording observations**

The Investigator or a person under his/her direct supervision will be responsible for implementing the Study Protocol, making observations, collecting samples, and recording data during the clinical field trials. After the data have been collected and recorded on the forms, the Investigator will send the data to the Study Monitors who will 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 an annual report that will be submitted to the FDA.

## G. Data storage

The Investigator is responsible for complete and accurate data collection. The Investigator is also responsible for archiving a complete set of all original data (with the exception of Form 1, in which case the original is forwarded to FDA through the Study Monitor, See Section VII.A.6. Accountability page 5 for complete details). Original raw data on Forms 2 and 4 will be retained by the Investigator until completion of the study, at which time copies will be sent to the Study Monitors. Copies of Form 3 will be sent to the Study Monitors on a quarterly basis. The Study Monitors will carefully check each set of data for accuracy and completeness. If there are any discrepancies in the data, the Study Monitor will contact the Investigator immediately to rectify the problem. After review, Study Monitors will forward all data to the Study Director. As stated above, the complete set of raw data will be archived by the Investigator. All data should be stored in a secure place. Another complete data set (copies) will be archived by the Study Director.

## XVIII. PLANS FOR DATA ANALYSIS

Data analysis will be completed by the Study Director located at the Bozeman National INAD Office. Data from the treatment year will be summarized through tabulation and appropriate statistical analysis. An annual report will be prepared for submission to the Sponsor who will in turn submit the report to the FDA. This submission will probably include a request for an extension of the INAD based on the data collected during that year. When sufficient data are collected, the entire INAD data set will be summarized in a final report for submission to support a full NADA.

## XIX. PROTOCOL AND PROTOCOL AMENDMENTS

A signed copy of the Study Protocol must be retained by each Investigator. At any time before a study begins, desired changes in the Study Protocol should be brought to the attention of the Study Director. The desired changes will be fully described in the form of an amendment along with the reason for the change. The amendment will be signed by the Sponsor (or its representative). Copies of the signed amendment will be attached to each copy of the Study Protocol. Investigators will be liable for non-compliance violation if drugs are used without a Study Protocol or differently than specified in the Study Protocol, if forms are not filed on time, or if the study data are not properly collected, maintained, and reported. The Study Monitor is responsible for determining if all the INAD procedures are being followed as defined by the Study Protocol.

## XX. PROTOCOL DEVIATIONS

Deviations from the established Study Protocol occasionally cannot be avoided. If deviations occur, the Study Monitor should be contacted immediately for advice. Protocol deviations should be fully documented and should be accompanied by a written explanation of what

happened, why, and what steps were taken to mitigate the deviation. Deviation statements should be signed and dated. These statements should be forwarded to the Study Monitor along with the quarterly data summaries and ultimately be submitted to the Study Director.

## LITERATURE CITED

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- Hoar, W.S. 1969. Reproduction. In: Fish Physiology Volume III. Eds. W.S. Hoar and D.J. Randall. Academic Press, New York and London. pp.1-72
- Houssay, B.A. 1931. Action sexuelle de l'hypophyse sur les poissons et les reptiles. C.R. Seances Soc. Biol. Ses Fil. 106:377-378
- Pickford, G.E., and J.W. Atz. 1957. The Physiology of the Pituitary Gland of Fishes. New York Zoological Society, New York. pp. 613
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