

**STUDY PROTOCOL FOR A COMPASSIONATE AQUACULTURE
INVESTIGATIONAL NEW ANIMAL DRUG (INAD)
EXEMPTION FOR CHANNEL CATFISH PITUITARY
(CP) UNDER INAD #11-468**

Sponsor:

U.S. Fish and Wildlife Service, Fisheries and Habitat Conservation

Sponsor Signature

Date Approved

Manufacturer/Supplier:

Hybrid Catfish Company
1233 Montgomery Drive
Inverness, MS 38753

Facility for Coordination of CP INAD:

USFWS's Aquatic Animal Drug Approval Partnership Program
Bozeman National INAD Office
4050 Bridger Canyon Road
Bozeman, Mt 59715

Proposed Starting Date

April, 1 2006

Proposed Ending Date

March 31, 2010

Study Director

Dr. David Erdahl

Study Director Signature

Date

Clinical Field Trial Location and Trial Number:

Type or Print Facility Name

Investigator _____

Type or Print Name

Investigator Signature

Date

STUDY PROTOCOL FOR A COMPASSIONATE AQUACULTURE INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR CHANNEL CATFISH (*Ictalurus punctatus*) PITUITARY (CP) UNDER INAD #11-468

I. STUDY ID AND TITLE

Clinical field trials to determine the efficacy of channel catfish (*Ictalurus punctatus*) pituitary (CP) to induce gamete maturation (ovulation and spermiation) in a variety of catfish species. INAD #11-468.

II. SPONSOR

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Study Director: Mr. Jim Bowker, U.S. Fish and Wildlife Service, Aquatic Animal Drug Approval Partnership (AADAP) Program, 4050 Bridger Canyon Road, Bozeman, MT 59715; Phone: 406-994-9910; Fax: 406-582-0242; Email: jim_bowker@fws.gov

Principal Regional INAD Coordinators: Not applicable for this INAD.

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

III. INVESTIGATORS/FACILITIES

See Appendix IIIa for names and addresses.

IV. PROPOSED STARTING AND COMPLETION DATES:

Proposed Starting Date: April 1, 2006

Proposed Completion Date: March 31, 2010

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. It is also important to other federal, state, tribal, and private aquaculture programs throughout the United States.

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). 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, common carp pituitary (CCP) is the most widely used material to induce final gamete maturation (spawning) in fish. The use of CCP was first reported in the United States by Hasler et al., (1939; 1940), and is still widely used today, particularly in cool- and warmwater species.

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.

Channel catfish (*Ictalurus punctatus*) pituitary (CP) has also been found to be similarly effective in inducing ovulation and spermiation (Sneed and Clemens, 1960; and Clemens and Sneed, 1968). Although CP has not been widely used to date, it is easily obtainable, and may in fact offer some advantages as compared to CCP with respect to specific use in catfish species.

The purpose of this compassionate INAD for CP is to develop clinical field trial data that will be used to determine the efficacy and appropriate treatment regimes for use of CP to induce ovulation and/or spermiation in a variety of cultured catfish species. These data will be used to support a new animal drug application (NADA) for CP, to petition that CP be considered a low regulatory priority compound, or to support "indexing" of CP under the Minor Use and Minor Species (MUMS) Animal Health Act of 2004 (note: as established in Section 572 of the MUMS act). The USFWS believes that data from at least 2 -3 treatment seasons will be required in order to adequately assess the efficacy and safety of CP treatment.

VI. SPECIFIC OBJECTIVES

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

1. Collect scientific data necessary to establish the efficacy of CP on gamete maturation in a variety of catfish species.
2. Provide the opportunity for fish culturists to legally use CP to maintain the genetic integrity and improve the reproductive potential of hatchery broodstocks during the period of time necessary for: 1) the collection of efficacy and safety data required to support an NADA for CP; or 2) the collection of efficacy and safety data for use to petition CVM to consider the inclusion of CP on the list of Low Regulatory Priority Compounds (as per FDA Guide 1240.4200); or 3) or the collection of efficacy and safety data to support "indexing" of CP under the Minor Use and Minor Species (MUMS) Animal Health Act of 2004.

VII. MATERIALS

A. Test and control articles:

1. Drug Identity

a. Active ingredient

Common Name: Channel Catfish Pituitary (CP)

C.A.S Registry No: None

Appearance: Brownish/White powder

Odor: None

b. Strength and dosage form

CP is obtained by dissection as a fresh material from adult channel catfish (*Ictalurus punctatus*). Whole pituitaries are desiccated using an alcohol/acetone rinse, ground into a powder, and stored in sterile vials. CP is prepared for injection by suspending the powder in sterile physiological saline.

c. Manufacturer, source of supply

Hybrid Catfish Company
1233 Montgomery Drive
Inverness, MS 38753

Contact: Roger Yant
Ph: 662-265-5308
Fax: 662-207-0461
Email: yant@technoinfo.com

2. Verification of drug integrity/strength:

The Manufacturer/Supplier will provide the documentation necessary to establish purity of each lot of CP supplied. The lot number and date of processing for each batch of CP 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 CP-1) will clearly identify the lot number of all CP shipments. If the integrity of the CP 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 CP-2). The Study Monitor assigned to the Investigator involved will be immediately notified.

3. Storage Conditions

CP 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 CP 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"*. CP 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 **Common Carp Pituitary** (CCP; see Appendix IV). Although a MSDS for CP is not available at this time, CCP is considered to be a near-identical compound. Each person involved with the study and each person who may be present during the use of CP shall be required to read the CCP MSDS. Safety precautions as outlined in the CCP MSDS will be followed at all times when working with CP.

5. Investigational labeling

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

6. Accountability

Hybrid Catfish Company will be the sole supplier of CP to all Investigators under INAD 11-468.

Immediately upon receiving an order/shipment of CP, the Investigator will complete Form CP-1 "Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals". The investigator will archive the original in the facilities INAD file, and send a copy to his/her Study Monitor. Both the Investigator and the Study Monitor are required to sign Form CP-1. The Study Monitor will then forward a copy to the Study Director at the Bozeman National INAD Office. The Study Director will

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

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

7. Preparation Procedures

CP for injection will be supplied in vials containing 1 g of dessicated powder. CP is prepared for injection by suspending the powder in sterile physiological saline. The amount of CP needed for each treatment will be weighed on an accurate laboratory scale, preferably to the nearest milligram. Dilution volume will be dependent upon target 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 CP INAD 11-468 will need to complete several forms. These forms are described in Section XIII (p. 9). Copies of these forms are attached to this Study Protocol.

VIII. EXPERIMENTAL UNIT

The experimental unit in this clinical field trial will consist of a contained or isolated group of fish. This will generally be a group of fish contained in a tank, raceway, or pond. In some cases the experimental unit may 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 CP can be ordered and dispensed under this INAD. Last minute deviations can be requested by the Sponsor, Study Director, or by an Investigator if emergency use-pattern needs should arise (See Section XX, p.12).

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

C. Period of use

CP treatment is most likely to be most effective when administered during the final stages of gamete maturation. In most cases, CP will be used within 4 weeks of the time fish are normally (i.e., historically) expected to spawn.

D. Environmental conditions

Environmental conditions during treatment will be variable and include a broad spectrum of water temperatures and water quality parameters. Environmental conditions should be reported on Form CP-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 CP-W. *Worksheet for Designing Individual Field Trials* that details each planned, specific treatment event. The worksheet should be filled out, signed, and sent by Fax to the Study Monitor. The Study Monitor will review the planned treatment (i.e. Worksheet), sign it, and forward (e.g. Fax) the Worksheet to the Bozeman NIO. The Bozeman NIO will review the Worksheet, assign the approved treatment a Study Number, and then notify both the Investigator and the Study Monitor of the assigned Study Number and approval to proceed. In most cases, this entire process should be able to be accomplished within a single working day. The Investigator should record the assigned Study Number on Forms CP-1, CP-2, CP-3, and CP-4N 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 National INAD Office for a study number and permission to proceed.

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. Non-treated control groups will not be a requirement for clinical field trials evaluating the efficacy of CP treatment conducted under this study protocol for INAD 11-468

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, to petition that CP be considered a low regulatory priority compound, or to support "indexing" of CP under the Minor Use and Minor Species (MUMS) Animal Health Act of 2004.

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

CP should be dissolved in sterile physiological saline and administered as either an intraperitoneal (IP) or intramuscular (IM) injection. IM injections will typically be administered anterior and lateral (on either side) to the dorsal fin. IP injections will typically be administered anterior to either pelvic fin.

B. Dose to be administered

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

C. Dosing interval and repetition

Dependent upon the species/strain of catfish involved in a trial, CP may be administered as either a single treatment (i.e., injection), or as a multiple treatment. Determination of whether a single or multiple treatment regimen is used will be largely a matter of past experience of the investigator and any literature citations reporting successful protocol with respect to specific species/strains. It is anticipated that a multiple treatment regimen consisting of a single "priming" dose (2 mg/kg) followed by a single "resolving" dose (8 mg/kg; administered approximately 12 hrs later) will be most often used.

D. Drug preparation procedures

CP for injection will be supplied in vials containing 1 g of a dessicated brownish/white powder. CP will be prepared for injection by suspending the powder in sterile physiological saline. The amount of CP needed for each treatment will be weighed on an accurate laboratory scale, preferably to the nearest milligram. Dilution volume will be dependent upon target 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 CP 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 CP treatment 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 that indicate 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 CP-3. Treatment response parameters that should be addressed include the following:

1. Primary Parameters

The primary response parameter for evaluating the effect of CP 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. In most situations, it is anticipated that treated fish should ripen within 3-5 days of initial treatment.

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 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 response/behavior by the fish or hazards to the applicator and/or other fish culture personnel. To date, CP has not been widely used in aquaculture. Although CCP (which is most likely a very similar compound) has been used extensively with beneficial effect and no adverse effects in fish culture for over 50 years, it is possible that adverse reactions to CP may occur under certain environmental conditions or with respect to specific species/strains of fish. Carefully observe all treated fish for any signs of adverse reaction to treatment. The Investigator should carefully document all observations of adverse reactions on Form CP-3. 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 injection site. Necropsy results should be recorded on Form CP-4N: Necropsy Report Form.

XIII. FORMS FOR DATA COLLECTION

- Form CP-W. Worksheet for Designing Clinical Field Trials under Channel Catfish Pituitary (CP) INAD 11-468
- Form CP-1. Report on Receipt of Drug - Guide for Reporting Investigational New Animal Drug Shipments for Poikilothermic Food Animals
- Form CP-2. Drug Inventory Form
- Form CP-3. Results Report Form
- Form CP-4N: Necropsy Report Form.

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 3 days following CP treatment before they are released or allowed to enter the food chain. If fish are injected more than once, these requirements will be based on the date/time of final treatment.

No withdrawal period will be required for CP treated fish that will be illegal for harvest for 3 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 CP-3.

XVI. DISPOSITION OF INVESTIGATIONAL DRUG

CP will be used only in the manner and by the individuals specified in the Study Protocol. If any unused or out-dated CP 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 4) for information and details.

B. Study Monitors

Study Monitors are generally fish health professionals with experience in diagnosing and treating fish diseases, and the ability to monitor overall fish health with respect to ongoing fish culture practices. A study monitor should be assigned to each facility that is authorized to treat fish with CP under this INAD. 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 CP itself) are already available at each participating facility. 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 5).

D. Administrator of the drug

CP will be administered directly by the assigned Investigator (fish hatchery manager) or under the Investigator's direct supervision (see Appendix IIIa for names). CP 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 4) for details and Forms CP-W, CP-1, CP-2, CP-3, and CP-4N for actual forms to be used in field trials.

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. Note: If the Study Monitor does not believe all required information has been provided, or forms have not been satisfactorily completed, he/she should contact the Investigator and rectify the situation before forwarding the package to the Study Director.

G. Data storage

The Investigator is responsible for complete and accurate data collection. The Investigator is also responsible for archiving a complete set of all original data. A copy of Form CP-1 should be sent immediately to the Study Monitor, who will in turn forward a copy to the Study Director. Original raw data on Form CP-2 should be retained by the Investigator until completion of the calendar year, at which time copies should be sent to the Study Monitor. Original raw data on Form CP-3 should be retained by the Investigator until completion of the study, at which time copies should be sent to the Study Monitor. Original raw data on Form CP-4N should be retained by the Investigator, and copies of all forms appended to corresponding Form CP-3s. Study Monitors should carefully check each set of data for accuracy and completeness. If there are any discrepancies in the data, the Study Monitor should contact the Investigator immediately to rectify the problem. After review, Study Monitors should forward all data to the Study Director. As stated above, a complete set of raw data should be archived by the Investigator. All data should be stored in a secure place. Another complete data set (copies) will be archived by the Study Director.

Form CP-3 Results Report Form is to be completed no later than 30 days after a course of therapy is completed. The purpose of this form and supplementary data is to document the completion and results of the treatment. In addition to the data solicited by the form, attach original source data that may have been collected to document any treatment effects.

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 FDA. When sufficient data are collected, the entire INAD data set will be summarized in a final report for submission to support a full NADA, to petition that CP be considered a low regulatory priority compound, or to support "indexing" of CP under the Minor Use and Minor Species Animal Health Act of 2004.

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

XX. PROTOCOL DEVIATIONS

Deviations from the established Study Protocol occasionally cannot be avoided. If deviations occur, the Study Monitor should be notified immediately. **Protocol deviations should be fully documented and should be accompanied by a written explanation of what happened, why, and what steps were taken to mitigate the deviation.** Deviation statements should be signed and dated. These statements should be forwarded to the Study Monitor along with corresponding Form CP-3s, and ultimately be submitted to the Study Director.

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