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STUDY PROTOCOL FOR A COMPASSIONATE AQUACULTURE INVESTIGATIONAL NEW ANIMAL DRUG (INAD) EXEMPTION FOR BENZOAK VET® (benzocaine) (INAD #11-740)

Sponsor:

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

_____ _____

Sponsor Signature Date Approved

Manufacturer/Supplier:

Pharma Production AS/Riverence Brood LLC
120 State Ave NE
Olympia, WA 98501

Facility for Coordination of BENZOAK VET® INAD:

Aquatic Animal Drug Approval Partnership Program
U.S. Fish and Wildlife Service
4050 Bridger Canyon Road
Bozeman, MT 59715

Proposed Starting Date	August 1, 2009
Proposed Ending Date	December 31, 2027
Study Director	Ms. 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 BENZOAK VET® (benzocaine) UNDER INAD #11-740

I. STUDY IDENTIFICATION AND TITLE

Clinical field trials to determine the efficacy of BENZOAK VET® as an anesthetic for use in a variety of fish species. INAD #11-740

II. SPONSOR

Dr. Marilyn Blair, U.S. Fish and Wildlife Service, Branch Chief, Aquatic Animal Drug Approval Partnership Program, 4050 Bridger Canyon Road, Bozeman, MT 59715; Phone: 406-994-9904; Fax: 406-582-0242; Email: marilyn_j_blair@fws.gov

Manufacturer/Supplier: Pharma Production AS/Riverence Brood LLC
120 State Ave NE
Olympia, WA 98501

Contact Person at Riverence Brood LLC:

Jesse Trushenski
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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;
Phone: 406-994-9911; Email: paige_maskill@fws.gov

INAD Study Monitors: Appendix II will contain the names and addresses of the participating monitors that will be submitted directly to the Center of Veterinarian Medicine (CVM). This list is not available for the public.

III. INVESTIGATORS/FACILITIES

Appendix IIIa will contain the names and addresses of the participating facilities that will be submitted directly to CVM and appropriate drug sponsor. This list is not available for the public.

IV. PROPOSED STARTING AND COMPLETION DATES

Proposed Starting Date: August 1, 2009

Proposed Completion Date: December 31, 2027

V. BACKGROUND/PURPOSE

A. Background Information:

The use of anesthetics is an important tool with broad application to fisheries management programs. Most often, anesthetics are used to reduce stress associated with the handling and/or transportation of fish. Anesthetics are widely used both in the culture of captive populations, and in field situations that involve the management of wildstock fish populations. Although a number of compounds have been used in the past, currently, the only approved anesthetic for use on fish is SYNCAINE (active ingredient methane tricainesulfonate, ANADA 200-226). SYNCAINE has a withdrawal period of 21 days. This restriction requires that potential food fish must be held for a minimum of 21 days following treatment before they can be released for legal harvest or slaughtered. While both of these products have been found to be effective anesthetics for use in fish, their required 21-day withdrawal period severely restricts approved use in many situations. In contrast, a shorter withdrawal anesthetic would allow food fish to be released, stocked, or slaughtered sooner than the approved anesthetics following treatment. In numerous fisheries management and aquaculture programs there is a critical need for such an anesthetic. BENZOAK VET® has been developed and approved in Norway as an anesthetic for use on salmon and trout.

The active ingredient in BENZOAK VET®, benzocaine, is a local anesthetic commonly used as a topical pain reliever for insect bites, minor burns, small wounds, or other skin irritations. Benzocaine is the active ingredient in many over-the-counter anesthetic ointments.

B. Purpose of INAD:

The purpose of this compassionate INAD for BENZOAK VET® is to develop clinical efficacy field trial data that will be used to determine the most appropriate treatment regimen for BENZOAK VET® for use as an anesthetic in a variety of fish species. These data will be used to support a new animal drug application (NADA) for BENZOAK VET®.

The U. S. Fish and Wildlife Service (USFWS) anticipates requesting the U. S. Food and Drug Administration (FDA) to grant extensions of this INAD for additional years. The USFWS believes that data from at least 3 - 5 treatment seasons will be required in order to adequately assess the efficacy of BENZOAK VET® as an anesthetic for use in fish, and to collect sufficient data 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 effectiveness of BENZOAK VET® as an anesthetic in a variety of fish species under a variety of environmental conditions (e.g., temperature, salinity, water hardness, pH, etc.)

2. Provide an opportunity for fish culturists and fisheries managers to legally use BENZOAK VET® as an anesthetic so that they can maintain and manage healthy stocks of fish during the period of time necessary for collection of efficacy, safety, and residue data required for an NADA for BENZOAK VET® in fish

VII. MATERIALS

A. Test and control articles:

1. Drug Identity

a. Active ingredient

Chemical Name:	benzocaine (benzocainum-Ethyl p-aminobenzoate)
C.A.S. Registry No.:	94-09-7
Molecular Weight:	165.189 g/mol.
Appearance:	Blue/green liquid
Odor:	Very slight spicy, pungent odor
Specific Gravity:	1.035

b. Strength and dosage form

BENZOAK VET® is 20% benzocaine (active ingredient). Fish are exposed by immersion bath.

c. Manufacturer, source of supply

Pharma Production AS/Riverence Brood LLC
120 State Ave NE
Olympia, WA 98501

Contact Person at Riverence Brood LLC:

Jesse Trushenski
Phone: 618-559-9397
Email: jesse.trushenski@riverence.com

2. Verification of drug integrity/strength:

The distributor (STIM AS) will provide the analytical data necessary to establish the purity of each lot/batch of BENZOAK VET® supplied (i.e., a Certificate of Analysis and a Certificate of Conformance). The lot number and date of manufacture for each batch of BENZOAK VET® 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 BZK-1) will clearly identify the lot number and date of manufacture of BENZOAK VET® shipments. If the integrity of the BENZOAK VET® is compromised (i.e., by spilling or contamination of the stock container) the event will be carefully recorded, dated, and signed in the Drug Inventory Form (Form BZK-2). All unusable BENZOAK VET® will be disposed of by following the Safety Data Sheet (SDS).

3. Storage Conditions

BENZOAK VET® will be stored in the original container supplied by the Manufacturer with the appropriate investigational label attached. BENZOAK VET® has high stability and should be stored at room temperature in a dry location away from direct sunlight. BENZOAK VET® should be stored in a secure location such as in a locked cabinet.

4. Handling Procedures

Each Study Monitor and Investigator will be required to have a current copy of the SDS for BENZOAK VET® (Appendix IV). Each person involved with the study and each person who may be present during the use of BENZOAK VET® shall be required to read the SDS. Safety precautions as outlined in the SDS will be followed at all times when working with BENZOAK VET®. Standard laboratory equipment such as gloves, lab coats or aprons, eye protection, etc., will be worn at all times.

5. Investigational labeling

A copy of the label to be attached to each container of BENZOAK VET® is provided in Appendix V. Although investigational labels will be affixed to BENZOAK VET® containers by the supplier (i.e., the US Agent, Riverence Brood LLC), it is the responsibility of the Investigator to ensure proper labeling of all containers of BENZOAK VET®.

6. Accountability

Riverence Brood LLC will be the sole supplier of BENZOAK VET® to all Investigators under this INAD.

1. All facilities using BENZOAK VET®:

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

All Investigators are also responsible for maintaining an accurate inventory of BENZOAK VET® on-hand. A Drug Inventory Form (Form BZK-2) must be completed and maintained by each Investigator. Each time BENZOAK VET® 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 BENZOAK VET® will be disposed of by following the SDS (note: unless BENZOAK VET® is planned for use in another approved field trial, and planned usage is within the storage guidelines established by the manufacturer). Disposition of all BENZOAK VET® must be properly recorded and accounted for on the Drug Inventory Form (Form BZK-2). The Study Monitor will be responsible for verifying the quantity of BENZOAK VET® remaining on hand versus the amount indicated on Form BZK-2. **Note:** BENZOAK VET® can be transferred to other facilities that are participating under INAD 11-740. Transfers must be shown on Form BZK-2.

7. Preparation Procedures

BENZOAK VET® will be prepared according to label directions for normal use. This includes accurately measuring (volumetrically) the calculated amount of BENZOAK VET® to obtain the desired dose. BENZOAK VET® should be added directly to the full-volume of water in the treatment tank. Immediately after the addition of BENZOAK VET® to the treatment tank, mix thoroughly to ensure uniform distribution of anesthetic. Note: Do not make a concentrated stock of solution of BENZOAK VET® before actual use.

B. Items Needed for Treatment, Sample Collection, Observations, Etc.:

Treatment and diagnostic equipment should include a balance, graduated cylinder or flask, treatment tank, recovery tank, thermometer, stopwatch, and a dissolved oxygen meter.

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

VIII. EXPERIMENTAL UNIT

The experimental unit in this clinical field trial 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. This protocol is not approved for treatments in the field that would require immediate release.

IX. ENTRANCE CRITERIA

A. Facilities/Investigators

The proposed facility and the Investigator must be listed in Appendix IIIa (note: this appendix is only available for AADAP; CVM; and the appropriate drug sponsor) of this Study Protocol for the current calendar year before BENZOAK VET® can be ordered and dispensed under this INAD. Last minute deviations can be requested by the Sponsor, Investigator, or Study Monitor in case emergency use-pattern needs should arise (See Section XX). However, poor planning and/or a lack of preparation will not be considered an emergency situation.

B. The characteristics of the study animals (species, number, etc) in Appendix VIb will be sent directly to CVM. This list is not available for the public.

C. Environmental conditions

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

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

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

Prior to initiating each treatment event, the Investigator must first complete Form BZK-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 BZK-2 and BZK-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*** *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.*

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 BENZOAK VET® as an anesthetic. As the primary use of BENZOAK VET® will be to facilitate handling and reduce stress to fish when they are being handled, untreated controls would in most cases be extremely impractical, as well as detrimental to fish health. However, Investigators are encouraged to record observations with respect to the behavior and physiological state of fish prior to BENZOAK VET® treatment. This information will provide a "psuedo-control" as to fish condition without, or prior to, BENZOAK VET® treatment.

C. 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 BENZOAK VET®. 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

BENZOAK VET® will be administered as a static immersion bath treatment. BENZOAK VET® will be prepared according to label directions for normal use. Dependent upon the desired dosage, the calculated amount of BENZOAK VET® necessary to achieve

the target dosage of benzocaine should be accurately measured (volumetrically). BENZOAK VET® should be added directly to the full volume of water in the treatment tank. Immediately after the addition of BENZOAK VET® to the treatment tank, mix thoroughly to ensure uniform distribution of anesthetic. Note: Do not make a concentrated stock of solution of BENZOAK VET® before actual use.

B. Dose to be administered and duration of treatment

BENZOAK VET® should be applied as a static immersion bath at benzocaine concentrations ranging from 10 - 100 mg/L (**note: BENZOAK VET® is 20% benzocaine as the active ingredient**) for up to 15-minute exposure. Treatment durations will not exceed 15 minutes. If fish do not become sedated to the desired level of anesthesia within 15 minutes, then treatment must be stopped. Investigators will need to decide if a higher dose is needed to achieve the correct level of anesthesia within the 15-minute time frame before continuing treatments. After completion of treatment and handling, fish should immediately be placed in fresh water (i.e., culture water not containing BENZOAK VET®).

Within this range, the actual concentration applied will be at the discretion of the Investigator. Dosage will likely vary with respect to species, water temperature, and level of anesthesia desired.

> Note: the term **Handleable** (or a handleable level of sedation) is used to describe sedation that is typically used when handling fish (i.e., lengths and weights; spawning; Floy tags; PIT tags; etc).

C. Dosing interval and repetition

BENZOAK VET® will be applied as a single treatment event and will not require repeated treatments. Treatment baths will not be re-dosed, so new treatment baths will need to be made once it is determined that additional baths of fish are no longer becoming sedated in the expected timeframe. Fish will only be treated a single time that day.

D. Disposition of anesthetic solution

If at all possible, discharge of anesthetic solution remaining in the treatment containers following completion of treatment should be to the ground. If ground discharge is not possible, anesthetic solution may be released/mixed with facility effluent. In situations where minimal dilution of anesthetic solution occurs prior to release to public surface waters, a pulsed release of anesthetic solution should be employed to minimize discharge levels.

E. Detailed procedures for drug administration

Appropriate personal protective equipment (e.g., gloves, protective apparel, eye protection) should be worn at all times when working with BENZOAK VET®. The amount of BENZOAK VET® necessary for each treatment should be accurately measured volumetrically immediately prior to treatment. BENZOAK VET® should be

added directly to the full volume of water in the treatment tank. Immediately after the addition of BENZOAK VET® to the treatment tank, mix thoroughly to ensure uniform distribution of anesthetic. Note: Do not make a concentrated stock of solution of BENZOAK VET® before actual use.

F. 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 minimize changes in fish cultural procedures or environmental conditions and apply no other treatments following treatment with BENZOAK VET®.

An exception to this is AADAP has requested the food use authorization to allow for the use of certain drug treatments with BENZOAK VET® treatments, provided the withdrawal time and use pattern identified in the food use authorization for that concomitant treatment is observed (see section XV for specific concomitant treatment information). The drugs must be used under the conditions of the respective INAD protocol or approved labeling. If another drug is used, please note its use on Form BZK-3 under the description of results section. **Please consult the Study Director to find out if BENZOAK VET® can be used with another drug prior to treatments.**

XII. TREATMENT RESPONSE PARAMETERS

The collection and reporting of source data begins with the decision to treat valuable fish based on hatchery records or field management practices 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 BZK-3. Treatment response parameters that should be addressed include the following:

1. Primary Response Parameters

The primary treatment response parameters in this study will be a reflection of the physiological condition of fish following treatment with BENZOAK VET®. The primary physiological conditions evaluated will include when a fish is considered to be: “handleable” and “recovered”. Data should be reported in time (minutes) to reach handleable, how long fish were held in the treatment bath, and time to recovery from sedation.

Handleable

A fish will be considered handleable when it loses partial or total equilibrium, has slow but regular opercular rate, can be caught easily by hand, placed on a measuring board with minimal fish movement, and easily measured for length. As a general rule, a fish will be considered handleable when it can be captured and held for several seconds without

difficulty. This is similar to Stages 3 - 4 of anesthesia as described by Summerfelt and Smith (1990).

The handleable level of sedation will be used for insertion of PIT, coded, or floy tags; length and weight measurements; spawning; and other fish handling procedures that don't require surgery.

Recovered

A fish will be considered recovered from anesthesia when it exhibits normal swimming behavior, including avoidance of obstacles. For this study, the fish must recover in less than 30 minutes of exposure to fresh water to be considered "recovered".

As a result of the potential diversity of treatment conditions that may be involved in these studies, Investigators are encouraged to provide detailed descriptions of all study variables, including specific definitions/descriptions of level of anesthesia and criteria used to establish anesthesia level. Investigators may also choose to create their own forms for purposes of recording source data under this INAD. **Supplementary data forms should be attached to Form BZK-3.**

2. Secondary Response Parameters

Secondary parameters include general observations on fish behavior and response to routine culture/management activities. Secondary parameters would include such responses as feeding activity, apparent level of stress, or other negative fish behavior (including, but not limited to, gill coughing, agitation, and/or jumping when exposed to treatment). All post-treatment mortality should be documented.

3. Adverse Drug Events

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 changes in water quality, negative responses/behavior by the fish (e.g., gill coughing, agitation, and/or jumping when exposed to treatment) or hazards to personnel. All adverse drug events must also be documented on Form BZK-3. It is possible adverse drug events may occur under certain environmental conditions or with respect to specific species/strains of fish. Careful observation of all treated fish for signs of any adverse reaction to treatment is extremely important, and all observations of adverse drug events should be documented. 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 BENZOAK VET® INAD will need to complete the following forms:

Form BZK-W. Worksheet for Designing Individual Field Trials - located in the New Study Request tab

Form BZK-1. Report on Receipt of Drug – located in the Manage/View Drug Inventory tab

Form BZK-2. Chemical Use Log for Field Trials under BENZOAK VET® under INAD #11-740 – located in the Manage/View Drug Inventory tab and filled out in Form BZK-3 to show use

Form BZK-3. Results Report Form for use of BENZOAK VET® under INAD #11-740 – located in the Active Studies table on the home page

Copies of these forms are attached to this Study Protocol. Actual reporting is accomplished on forms located in the online INAD database.

XIV. RECORD KEEPING PROCEDURES

As stated immediately above, all data reporting is 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 Study Director. **Note:** 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.

XV. DISPOSITION OF INVESTIGATIONAL ANIMALS

Animals that die during treatment should be disposed of by burial or incineration.

All fish treated **must be held for at least 72 hours** following treatment with BENZOAK VET® before they are stocked or allowed to enter the food chain.

Fish that are illegal for harvest during that 72-hour period may be released immediately after treatment.

For treatments where other drugs may be used at the same time as BENZOAK VET® then the longest withdrawal period must be followed. See below for the drugs listed on the current food use authorization request and the withdrawal period that must be followed. Contacting AADAP before use of a concomitant drug is advised.

1. The use of Chorulon® needs to follow the approved label dosing instructions for this drug. A 72-hour withdrawal period is required for use of BENZOAK VET® and Chorulon®.
2. The use of CCP is used under the conditions of INAD 8391. A 72-hour withdrawal period is required for use of BENZOAK VET® and CCP.
3. The use of GnRH IIa is used under the conditions of INAD 13-345. A 72-hour withdrawal

period is required for use of BENZOAK VET® and GnRH IIa.

4. The use of LHRHa is used under the conditions of INAD 8061. A 72-hour withdrawal period is required for use of BENZOAK VET® and LHRHa.
5. The use of sGnRHa (Ovaplant-L) is used under the conditions of INAD 13-298. No fish can be released if Ovaplant-L is used since there is no food use authorization in place for this INAD.
6. The use of oxytetracycline injectable is used at 20 mg/kg body weight. A 45-day withdrawal period is required for use of BENZOAK VET® and oxytetracycline injection.
7. The use of erythromycin is used under the conditions of INAD 12-781 and is only for salmonid species. A 60-day withdrawal period is required for use of BENZOAK VET® and erythromycin.

The Investigator must record the disposition of all treated fish on Form BZK-3.

XVI. DISPOSITION OF INVESTIGATIONAL DRUG

BENZOAK VET® will be used only in the manner and by the individuals specified in the Study Protocol. If any unused or outdated BENZOAK VET® 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 SDS located in Appendix IV of this protocol. Disposition of all BENZOAK VET® must be properly recorded and accounted for on the Chemical Use Log (Form BZK-2). The Study Monitor will be responsible for verifying the quantity of BENZOAK VET® remaining on hand versus the amount indicated on Form BZK-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 BENZOAK VET® is planned for use in another approved field trial, and planned usage is within the storage guidelines established by the manufacturer).

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

A. Drug distribution

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

B. Study Monitors

The Study Monitors are generally fish health professionals with experience in diagnosing and treating fish diseases. A Study Monitor will be selected by each facility that is authorized to treat fish with BENZOAK VET® under this INAD. 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 BENZOAK VET® itself) are already available at each participating facility. The use of anesthetics to aid in the handling of fish is a common occurrence at most fish hatcheries and

in many fisheries management programs. Fish hatchery/farm managers and fisheries managers (i.e., Investigators) are well trained and well equipped to supervise these procedures (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

BENZOAK VET® will be administered directly by the assigned Investigator (fish hatchery/farm manager or fisheries manager) or under the Investigator's direct supervision. BENZOAK VET® 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: Form BZK-W, Form BZK-1, Form BZK-2, and Form BZK-3.

F. Recording observations

The Investigator or a person under his/her direct supervision will be responsible for implementing the Study Protocol, making observations, collecting samples, and recording data during the clinical field trials. After the data have been collected and recorded on the forms, the Investigator will send the data to the Study Monitor who will ensure that all required information is provided. The Study Monitor will in turn send the data to the Study Director. The Study Director will analyze and summarize the data and prepare summary reports 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 protocol 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. 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.

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. **The requested changes cannot occur until FDA concurrence has been received**. 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 ensuring that all INAD procedures are being followed as defined by the Study Protocol.

XX. PROTOCOL DEVIATIONS

Deviations from the established Study Protocol occasionally cannot be avoided. If deviations occur, the Study Monitor should be contacted immediately 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.** These statements should be forwarded to the Study Monitor along with Form BZK-3, and ultimately be submitted to the Study Director.

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.

References

Summerfelt, R.C. and L.S. Smith. 1990. Anesthesia, surgery, and related techniques. In: Methods for Fish Biology. C.B. Schreck and P.B. Boyle editors. American Fisheries Society. Bethesda, Maryland. pp. 213-272

Appendix I. Sponsor Contact Information for BENZOAK VET® INAD #11-740

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

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

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

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

1 Appendix II. Study Monitors for BENZOAK VET® INAD #11-740

Note: This information will be provided directly to CVM

11Appendix IIIa. Facilities and Names of Investigators Participating under ® INAD #11-740

Note: This information will be provided directly to CVM and Riverence Brood LLC

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 fish biology, fish behavior, and water chemistry sufficient to apply sedative/anethestic treatments to fish.

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 BENZOAK VET® INAD #11-740

The SDS for BENZOAK VET® can be found at the drug sponsor's website: Benzoak Vet SDS EN 2021.pdf

Appendix V. Investigational Label for BENZOAK VET® INAD #11-740

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 BENZOAK VET® INAD #11-740

All freshwater finfish

Freshwater prawn

All saltwater finfish

1Appendix VIb. Table of Facilities and Fish Stocks Treated under BENZOAK VET® INAD #11-740

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** d**atabase**. Any paper forms that are submitted to AADAP will be sent back to the study participants.

Form BZK-W: Worksheet for Designing Individual Field Trials under BENZOAK VET® INAD 11-740

INSTRUCTIONS

1. Investigator must fill out Form BZK-W for each trial conducted under this INAD **before** actual use of BENZOAK VET®. The Investigator is responsible that Form BZK-W is completed accurately.
2. Investigator should forward a copy of BZK-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 the Study Number.

SITE INFORMATION

Facility			
Address			
Investigator			
Reporting Individual (if not Investigator)			
Phone		Fax	

FISH CULTURE AND DRUG TREATMENT INFORMATION

Fish species			
Number of treated fish			
Average fish weight (gm)		Average fish length (in)	
Estimated total weight of fish treated (lbs)			
Intended level of anesthesia (Handleable - **H**)			
Intended dosage (mg benzocaine/L) – <100 mg/L		Planned duration of treatment (minutes) - <15 minutes	
Estimated total amount of BENZOAK VET® needed for proposed treatment (ml)			
Anticipated date treatment will be initiated			
BENZOAK VET® manufacturer	**ACD Pharma**	BENZOAK VET® lot number	

Worksheet for Designing Individual Field Trials

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

Study designed by _____

DISPOSITION OF TREATED FISH (Human Food Safety Considerations):

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

Note: Euthanized fish must not be sent to slaughter or be otherwise available for food. If another drug is used during the BENZOAK VET® treatment, then the longest withdrawal period must be followed – see section XV of the protocol.

☐ Investigator should initial here to indicate awareness that fish disposition must be in compliance with FDA-mandated withdrawal times as described in the Study Protocol.

WORKER SAFETY CONSIDERATIONS:

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

Date Prepared: _____ **Investigator:** _____

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

FORM BZK-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 BZK-1 **immediately** upon receipt of BENZOAK VET®.
2. Investigator should forward a copy of Form BENZOAK VET® 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	**BENZOAK VET®**	INAD Number	**11-740**
Proposed Use of Drug	Sedation/anesthesia in a variety of fish species		
Date of CVM Authorization Letter	September 9, 2009		
Date of Drug Receipt		Amount of Drug Received	
Drug Lot Number		Trial Number	
Name of Investigator			
Address of Investigator			
Location of Trial			
Pivotal Study	No	Non-pivotal Study	Yes
Approximate Number of Treated Animals		Approximate Number of Control Animals	
Study Protocol Number	11-740		
Approximate dates of trial (start/end)			
Species, Size, and Type of Animals			
Maximum daily dose and duration	100 mg/L benzocaine for 15 minutes		
Methods(s) of Administration	Immersion		
Withdrawal Period	72 hours If another drug is used with BENZOAK VET® then the longest withdrawal time is needed		

Date Prepared: _____ **Investigator:** _____

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

Date Reviewed: _____ **Study Director:** _____

Form BZK-2: Chemical Use Log for Use of BENZOAK VET® under INAD 11-740

INSTRUCTIONS

1. Investigator should initiate a new form BZK-2 **immediately** upon receipt of each shipment of BENZOAK VET®.
2. Each lot of BENZOAK VET® may be used for multiple treatment regimens.
3. Form BZK-2 should be updated whenever drug is used, transferred, or discarded.

Qty of BENZOAK VET® from previous page (ml) _____ Facility _____Reporting individual _____

Date	Amount of BENZOAK VET® received (ml)	Lot number of BENZOAK VET® received	Study Number	Amount BENZOAK VET® used in treatment (ml)	BENZOAK VET® transferred (ml)[1]	BENZOAK VET® discarded (ml)	BENZOAK VET® remaining on hand (ml)	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						

[1] **Unused BENZOAK VET® that is shipped to another facility participating in BENZOAK VET® INAD 11-740 (Note: BENZOAK VET® can only be shipped to another facility with prior authorization by the AADAP Office).**

1**Date Prepared:** _____ **Investigator:** _____

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

Form BZK-3: Results Report Form for BENZOAK VET® Use under INAD 11-740

INSTRUCTIONS

1. Investigator must fill out Form BZK-3 no later than 10 days after completion of the trial. Attach lab reports and other information.
2. If BENZOAK VET® was not used under the assigned Study Number, contact the Study Director at the AADAP Office on how to close-out the study.
3. Investigator should forward a copy of Form BZK-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

BENZOAK VET® lot number		Total amount of BENZOAK VET® used in treatments (ml)	
Fish species treated		Dosage used (mg/L benzocaine)	
Average fish weight (gm)		Average fish length (in)	
Total number of treated fish		Approximate fish age (fingerling/juvenile/adult)	
Treatment bath vol. (gal)		Number of fish/bath	
Treatment duration (minutes)		Treatment date(s)	

WATER QUALITY PARAMETERS

1Average treatment temp (°F)		Dissolved Oxygen (mg/L)	
pH		Hardness - $CaCO_3$ (mg/L)	

Anesthesia Record - Version 1

INSTRUCTIONS

1. Investigator should fill out the Anesthesia Record as completely as possible.
2. Enter the number of fish in the treatment tank at one time. Dependent upon the size of the tank, fish size, etc., this number could vary from 1 to 20 or possibly even higher.
3. Enter the level of anesthesia desired. Use "H" for handleable. If other measurements or parameters are used to determine level of desired anesthesia, describe anesthesia level in detail on a separate sheet of paper and attach to Form BZK-3.
4. Use additional copies of this form if more than 20 individual treatments are involved in the trial.
5. If a different dose or purpose (i.e., spawning, tagging, fish health) is needed then a different study number is needed.

Date	Treatment Number	Species	Fish per Treatment	Level of Anesthesia (H)	BENZOAK VET® Dose (mg/L)	Time to Anesthesia (min)	Time to Recovery (min)	Observer Initials
	1							
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
	11							
	12							
	13							
	14							
	15							

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? **Attach any supplemental reports.**

TOXICITY OBSERVATIONS: Report any apparent drug toxicity including a description of unusual fish

behavior.

OBSERVED WITHDRAWAL PERIOD OF TREATED FISH:

Observed withdrawal period: _____ **72 hrs**

_____ **If another drug was used during the BENZOAK VET® study then the longest withdrawal period needs to be followed – see section XV of the protocol.**

Note: Euthanized fish must not be sent to slaughter or be otherwise available for food.

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

NEGATIVE REPORT BENZOAK VET® was not used at this facility under this Study _____Number during the reporting period. The study will be closed out in the online INAD database.

Date Prepared: _____ **Investigator:** _____

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

NOTICES

Paperwork Reduction Act

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

ESTIMATED BURDEN STATEMENT

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

FREEDOM OF INFORMATION ACT STATEMENT

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