

**STUDY PROTOCOL FOR A COMPASSIONATE AQUACULTURE  
INVESTIGATIONAL NEW ANIMAL DRUG (INAD)  
EXEMPTION FOR OXYTETRACYCLINE USE  
FOR BATH MARKING (INAD # 9033)**

**Sponsor:**

U.S. Fish and Wildlife Service, Division of Fish Hatcheries

\_\_\_\_\_  
Sponsor Signature

\_\_\_\_\_  
Date Approved

**Manufacturer:**

Pfizer, Inc.  
1107 South 291 Highway  
Lee's Summit, MO 64081

**Facility for Coordination of Oxytetracycline for Bath Marking:**

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

Proposed Starting Date	April 11, 1995
Proposed Ending Date	April 10, 1996
Study Director	Mr. Jim Bowker

\_\_\_\_\_  
Study Director Signature

\_\_\_\_\_  
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 OXYTETRACYCLINE USE FOR BATH MARKING UNDER INAD #9033**

**I. STUDY ID AND TITLE**

Clinical field trials to determine the efficacy of oxytetracycline marking of cultured fish for use as a fishery management tool. INAD #9033

**II. SPONSOR**

Dr. David Erdahl, U.S. Fish and Wildlife Service, Branch Chief, Aquatic Animal Drug Approval Partnership Program, 4050 Bridger Canyon Road, Bozeman, MT 59715. Phone: 406/587-9265 ext. 125; FAX: 406/582-0242; Email: dave\_erdahl@fws.gov

**Manufacturer:** Pfizer, Inc  
1107 South 291 Highway  
Lee's Summit, MO 64081

**Study Director:** Mr. Jim Bowker, U.S. Fish and Wildlife Service, Aquatic Animal Drug Approval Partnership Program, 4050 Bridger Canyon Road, Bozeman, MT 59715. Phone: 406/587-9265 ext. 126; FAX: 406/582-0242; Email: jim\_bowker@fws.gov

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

**Study Monitors for Oxytetracycline 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 (9033) and a unique number for that facility (e.g., Bo Ginn NFH 9033 - 01).

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

Proposed Starting Date: April 11, 1995

Proposed Completion Date: April 10, 1996

## V. BACKGROUND/PURPOSE

Water soluble oxytetracycline is an effective and convenient marking agent for use on early life stages of fish. Extremely large numbers of fish can be marked simultaneously by simply exposing them to a uniform marking solution for up to several hours. In general, marking is accomplished by immersing very young fish in a bath containing 500 mg/L oxytetracycline and 1000 mg/L sodium chloride, buffered with Tris buffer to a Ph of 6.5 - 6.9, for six hours. Sodium chloride is necessary to prevent calcium chelation of the oxytetracycline. Oxytetracycline marking of fish is an extremely important fishery management tool

Because fish are generally crowded and held at high densities during oxytetracycline marking, great care must be taken to maintain water quality during treatment. Oxygen levels must not be allowed to drop below 5 ppm in treatment solutions, water temperature should be carefully controlled, pH buffers should be used to neutralize oxytetracycline acidity, and close attention must be paid to the capture and handling of the fish to minimize stress. Ideally, marking of young fish should be carried out in conjunction with routine hatchery operations (e.g. during transfer from the rearing facility to stocking sites several weeks after hatch (Secor et al. 1991 - attached as an addendum). As the use of oxytetracycline for marking increases, preliminary range-finding efficacy trials may be necessary for fish species or life-stages for which published marking methods or mark retention data does not already exist. Drug dosages, treatment schedules, fish handling methods and other variables may need to be tested. Complete documentation of well conceived studies will be of great value.

Specific procedures for marking fish with oxytetracycline will be designed to meet the needs of each species or lot, including the size and numbers of fish to be treated, the layout of the facility, fishery management needs, and environmental conditions. In all cases, the study objective will be to minimize the impacts of stress on fish health, fish quality and survival and to fully meet fishery management needs.

The purpose of this INAD is to develop clinical field trial data on the use of water soluble oxytetracycline as an agent for the non-intrusive marking of fish larvae, fry, or very young fish prior to, or shortly after, initiation of feeding. Fish of this size cannot be marked by fin clip or conventional tagging. Fish marked at this early life stage are not available for human consumption until they have grown to a much larger size, which would require at least a year or more after marking. Except for threatened and endangered species and research fish destroyed after use, no fish averaging larger than 2 grams each will be treated by oxytetracycline bath marking under this INAD exemption.

Because of life history patterns of the fish and harvest size regulations, no oxytetracycline-marked fish will be available for human consumption for at least one year after marking. These facts make oxytetracycline the marking agent of choice for use on large numbers of young fish. It fits in well with life cycle requirements of fish, routine fish cultural procedures, and presents virtually no human food safety risks. In most cases, immersion marking with oxytetracycline is the only practical means of permanently marking small fish for the evaluation of fishery management strategies.

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 is aware that oxytetracycline marking of some of the fish species listed in this INAD has never before been evaluated and new scientific ground is being broken by the studies proposed. There is no way of knowing in advance if, when, or where opportunities for pivotal studies will be encountered.

## VI. SPECIFIC OBJECTIVES

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

1. Collect scientific data necessary to establish the effectiveness of oxytetracycline bath marking of cultured fish species for use as a fishery management tool.
2. Provide an opportunity for USFWS fish culturists to legally use oxytetracycline for the bath marking of cultured fish species so that they can continue to meet fishery management objectives during the period of time necessary for collection of data that will be used to support an NADA for the use of oxytetracycline on fish.

Within these two relatively broad objective areas, there are also two more specific study protocol objectives. The two specific study objectives are described below:

### Objective A

Determine the efficacy of a **single** bath treatment of 500 mg of active oxytetracycline per liter of water for 6 hours for marking salmonid eggs and fry. An inherent withdrawal period of more than a year is assured by the fact that the life cycle of these fish will make them unavailable for harvest for a period of at least one year.

### Objective B

Determine the efficacy of a **single** bath treatment of 500 mg of active oxytetracycline per liter of water for 6 hours for marking eggs and larvae or fry of shad, striped bass, sturgeon, paddlefish, and other fish species listed in Appendix VI. After 30 - 40 days, juvenile fish may be harvested and released into public waters for fishery management purposes. However, an inherent withdrawal period of more than a year is assured by the fact that the life cycle of these fish will make them unavailable for harvest for a period of at least one year.

**Notice** - To ensure human food safety, reduce environmental concerns regarding the discharge of oxytetracycline, and reduce constraints on fish culture, the following guideline will be followed by all Investigators: **Except for threatened and endangered species and research fish destroyed after use, no fish averaging larger than 2 grams each will be marked by immersion in oxytetracycline solutions under this INAD exemption.**

## VII. MATERIALS

### A. Test and Control Articles:

1. Drug Identity
  - a. Active ingredient

Pfizer's over-the-counter Terramycin-343 soluble powder, containing 343 grams of active oxytetracycline hydrochloride per pound of product, will be the only form of the drug used by fish culturists to treat fish under this INAD. Terramycin-343 comes as an odorless, yellow crystalline powder that is moderately soluble in water. The physical and chemical properties of oxytetracycline are summarized in Appendix VIII.

b. Strength and dosage form

Drug baths will be given to provide a dosage of 500 mg of active oxytetracycline per liter of water for a duration of 6 hr.

c. Manufacturer, source of supply

Pfizer, Inc.  
1107 South 291 Highway  
Lee's Summit, MO 64081  
Ph. (816) 524-5580  
FAX: (816) 525-7360

2. Verification of Drug Integrity/Strength

Pfizer will provide limited analytical support in the event questions arise regarding product quality and drug activity.

3. Storage Conditions

Stocks of Terramycin-343 will be stored at temperatures and for periods of time as directed by label instructions.

4. Handling Procedures

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

The possible hazards associated with handling oxytetracycline and all associated equipment should be discussed, at least once per year, at station Safety meetings. Individuals with known allergic reactions to oxytetracycline will not be permitted to handle this compound. For transportation emergencies telephone CHEMTREC, 800/424-9300.

5. Investigational labeling

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

6. Accountability

Each USFWS Investigator will notify FDA prior to any shipment of oxytetracycline 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 water soluble oxytetracycline on hand. A Chemical Use Log (Form 2) will be supplied to each Investigator. Each time oxytetracycline is used, it must be reported by the Investigator on Form 2.

#### B. Items Needed for Sample Collection, Processing, and Mark Reading:

Sampling and diagnostic equipment should include standard dissecting equipment, as well as clean microscope slides, cover slips, and a fluorescent microscope. Generally, the procedures of Secor et al. (1991) will be used as a guide for sample processing and mark reading in clinical field trials conducted under this INAD. Both fish capture equipment and fish sampling/diagnostic equipment are routinely available at hatcheries. Microscopes should be equipped with 100 watt fluorescent bulbs and filter sets for wave lengths in the 360 nm range to enable reading of otoliths with little or no polishing.

When the Study Protocol has been approved and treatments are scheduled, the Investigator at each facility covered by the oxytetracycline for use in bath marking INAD will need to complete several forms. These forms are described in Section XIII (p 8). 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 could be a group of fish contained in a tank, raceway, or pond.

### IX. ENTRANCE CRITERIA

Entrance criteria for the use of oxytetracycline for bath marking are as follows:

1. The proposed facility and the investigator must be listed in Appendix IIIa of this Study Protocol before water soluble oxytetracycline can be ordered and dispensed under this INAD. Last minute deviations can be requested by the sponsor, by a proposed investigator, and/or the monitor (See Section XX).
2. Since the efficacy of oxytetracycline marking is being evaluated, Investigators **must** be prepared to document not only the success of the treatment (i.e. did treatment result in a clear, easily discernible otolith mark), but also fish cultural procedures prior to, during, and after the marking procedure.

Prior to initiating treatment, each Investigator must first complete a worksheet for study design pertaining to that specific treatment event (see Appendix VII). The worksheet should be filled out and sent by FAX to the Study Monitor. The Study Monitor will review the planned treatment, assign the approved treatment a Study Number, and then notify the Investigator to proceed. The Investigator should record the assigned Study Number on Form 3, as well as on any additional correspondence regarding that specific treatment event. If for some reason the Investigator is unable to reach his/her Study Monitor with regards to worksheet approval, they should contact the National INAD Office for permission to proceed.

## **X. Treatment Groups**

Separately confined, untreated, controls will not be required in the tests conducted to determine the effectiveness of oxytetracycline bath marking. Although untreated control groups are not a required element of treatment under this INAD exemption and are at the discretion of the Investigator, separately confined untreated controls are strongly encouraged whenever circumstances permit. Control groups are extremely important to not only document intended/expected response to treatment, but also to validate potential adverse reactions in treated animals. Control fish should be part the normal population being treated, and should be handled and held under the same conditions as treated fish. Use of control groups will ensure that results of efficacy studies provide useful information that will support a NADA. Whenever sufficient fish and rearing units are available, replicated groups of both treated and control should be used.

## **XI. TREATMENT SCHEDULES**

### Clinical Trials Addressing **Objective A**

#### A. Dosage and Duration

Oxytetracycline may be administered as a **single** bath treatment of 500 mg of active drug per liter of rearing water for 6 hours.

#### B. Fish species

Salmonid fish stocks listed in Appendix VI may be treated with oxytetracycline in clinical field trials under Objective A.

#### C. Treatment Schedule

According to Secor et al. (1991) the marking of fish larvae less than 10± days old is more effective than marking older juveniles. Secondly, marking should be scheduled to coincide with routine fish cultural practices such as moving fish from incubation/hatching facilities to rearing units. Fish can be marked during such transfer procedures with little extra effort and with little additional stress on fish. Because different early rearing procedures are used for different fish species, Investigators should describe in a step-wise manner, the way the marking procedure will be carried out (using the Worksheet for Designing Bath Marking Study Protocols).

### Clinical Trials Addressing **Objective B**

#### A. Dosage and Duration

Oxytetracycline may be administered as a **single** bath treatment of 500 mg of active drug per liter of rearing water for 6 hours.

#### B. Fish species

Non-salmonid fish stocks listed in Appendix VI may be treated with oxytetracycline in clinical field trials under Objective B.

### C. Treatment Schedule

According to Secor et al. (1991) the marking of fish larvae less than 10± days old is more effective than marking older juveniles. Secondly, marking should be scheduled to coincide with routine fish cultural practices such as moving fish from incubation/hatching facilities to rearing units. Fish can be marked during such transfer procedures with little extra effort and with little additional stress on fish. Because different early rearing procedures are used for different fish species, Investigators should describe in a step-wise manner, the way the marking procedure will be carried out (using the Worksheet for Designing Bath Marking Study Protocols).

## XII. TREATMENT RESPONSE PARAMETERS

The collection and reporting of source data begins with the decision to treat fish. Case history records, daily morbidity and mortality records, as well as any extenuating or mitigating circumstances that may affect treatment response need to be documented. Treatment response parameters that should be addressed include the following:

### 1. Primary Parameters

Primary parameters include the efficacy of the marking procedure, mark retention data (if possible), and morbidity and mortality data related to the marking procedure. Whenever possible, control fish should be included in the clinical field trial. These control fish should be part of the normal population and be held under the same conditions as the treated fish.

### 2. Secondary Parameters

Secondary parameters include general observations on the effect of treatment on fish behavior and response to routine culture activities. Secondary parameters 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 changes in water quality, extremely negative responses/behavior by the fish, or hazards to the applicator. There may be little information on the sensitivity of some fish species to oxytetracycline. 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 oxytetracycline for bath marking 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 oxytetracycline for bath marking under INAD #9033.
- Form 3. Diagnosis, treatment, and mortality record for clinical field trials using oxytetracycline for bath marking under INAD #9033.
- Form 4. Disposal record for animals from clinical field trials using oxytetracycline for bath marking under INAD #9033.

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. No withdrawal period will be required for treated eggs, fry, or larvae as an inherent withdrawal period of more than a year is assured by the fact that the life cycle of these fish will make them unavailable for harvest for a period of at least one year. No withdrawal period will also be required for dead fish that will be buried or rendered into non-edible products.

The Investigator must record the disposition of all treated eggs and/or fish on Form 4.

### **XVI. DISPOSITION OF INVESTIGATIONAL DRUG**

Oxytetracycline will be used only in the manner and by the individuals specified in the Study Protocol. If any unused or out-dated oxytetracycline 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 for each facility within the USFWS that is covered by the oxytetracycline for bath marking 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 oxytetracycline itself) are already available at each fish hatchery. Fish hatchery managers (i.e., Investigators) are well trained and well equipped to handle such cultural 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., page 5).

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

Oxytetracycline will be administered directly by the assigned Investigator (fish hatchery manager) or under the Investigator's direct supervision (see Appendix IIIa for names). Oxytetracycline 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 sends the data to the Study Monitors who ensure that all the information is provided. The Study Monitors 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 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). 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.

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

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

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

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

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

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

Knowledge of USFWS policy, programs, and organizational structure in order to be able to modify and adapt standard techniques/processes and to devise new strategies and plans necessary to overcome resource problems.

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



# MATERIAL SAFETY DATA SHEET

## SECTION 1 - CHEMICAL PRODUCT & COMPANY IDENTIFICATION

<b>Pfizer Inc</b>	<b>Emergency telephone</b>	1-800-228-5635
<b>Animal Health Group</b>	<b>Hours of operation</b>	24 Hours
<b>812 Springdale Drive</b>	<b>Telephone</b>	1-800-877-6250
<b>Exton, PA 19341</b>		

<b>Product name</b>	<b>TERRAMYCIN-343® soluble powder blend</b>
<b>Synonyms</b>	TERRAMYCIN-343® soluble powder blend; Oxytetracycline hydrochloride soluble powder blend
<b>Chemical family</b>	Tetracycline derivative
<b>Therapeutic use</b>	Antibiotic agent
<b>Description</b>	Yellow powder

## SECTION 2 - COMPOSITION/INFORMATION ON INGREDIENTS

<u>Hazardous Ingredient</u>	<u>CAS Number</u>	<u>Amount</u>
Oxytetracycline hydrochloride	2058-46-0	Trade Secret
Betaine hydrochloride	590-46-5	Trade Secret
Sucrose	57-50-1	Trade Secret

## SECTION 3 - HAZARDS IDENTIFICATION

<b>CERCLA ratings (scale 0-3)</b>	Health=1 Fire=0 Reactivity=0
<b>NFPA ratings (scale 0-4)</b>	Health=1 Fire=0 Reactivity=0
<b>Signal word</b>	<b>CAUTION!</b>
<b>Statements of hazard</b>	INFANTS OF MOTHERS EXPOSED DURING PREGNANCY MAY DEVELOP DISCOLORATION OF THE TEETH.
<b>Eye</b>	
<b>Short term effects</b>	None known; however, direct contact with any foreign material may cause eye irritation. Signs and symptoms might include redness, swelling, blurred vision or pain.
<b>Long term effects</b>	Not known or expected.
<b>Skin</b>	
<b>Short term effects</b>	May cause skin irritation.
<b>Long term effects</b>	Repeated or prolonged contact may cause dermatitis of the hands and wrists.
<b>Inhalation</b>	
<b>Short term effects</b>	May cause nose, throat and lung irritation.
<b>Long term effects</b>	Repeated or prolonged exposure may cause effects similar to those seen in clinical use. See "Ingestion" section, below.

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## SECTION 3 - HAZARDS IDENTIFICATION continued

### Ingestion

<b>Short term effects</b>	Ingestion of this material may cause effects similar to those generally seen in clinical use of antibiotics including gastrointestinal irritation, vomiting, transient diarrhea, nausea, and abdominal pain. Persons sensitive to this material or other materials in its chemical class may develop allergic reactions.
<b>Long term effects</b>	Symptoms of chronic exposure to tetracyclines include redness and swelling of the skin, rash, chills, yellowing of the skin and eyes, tooth discoloration, nausea, vomiting, diarrhea, stomach pain, and chest pain. Wheezing, asthma, low or high blood pressure, dizziness, lung congestion, blood changes (leukocytosis, atypical lymphocytes, toxic granulation of granulocytes and thrombocytopenia purpura), convulsion or shock may also occur.

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## SECTION 4 - FIRST AID MEASURES

<b>Eyes</b>	Immediately flush eyes with plenty of water. If irritation occurs or persists, get medical attention.
<b>Skin</b>	Wash skin with soap and plenty of water. Remove contaminated clothing and shoes. Wash clothing and thoroughly clean shoes before reuse. If irritation occurs or persists, get medical attention.
<b>Inhalation</b>	Remove to fresh air. If discomfort persists, get medical attention.
<b>Ingestion</b>	If swallowed, get medical attention immediately. Do not induce vomiting unless directed by medical personnel. Never give anything by mouth to an unconscious person.

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## SECTION 5 - FIRE FIGHTING MEASURES

<b>General hazard</b>	Toxic or corrosive emissions may be given off in a fire. See Hazardous combustion products, below, and Hazardous decomposition products in Section 10 - STABILITY AND REACTIVITY.
<b>Fire fighting instructions</b>	Wear approved positive pressure, self contained breathing apparatus and full protective turn out gear. Use caution in approaching fire.
<b>Extinguisher to use</b>	Use carbon dioxide, dry chemical, or water spray.
<b>Hazardous combustion products</b>	Emits toxic fumes of carbon monoxide, carbon dioxide, oxides of nitrogen, hydrogen chloride and other chlorine-containing compounds.
<b>Flash point</b>	Not applicable
<b>Autoignition</b>	Not applicable
<b>Minimum explosive concentration for dust/vapor</b>	Not known
<b>Flammability limits</b>	Not applicable

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## SECTION 6 - ACCIDENTAL RELEASE MEASURES

<b>Occupational spill</b>	Contain the source of spill or leak. Scoop spilled material into a labeled container for disposal. Avoid creating airborne dust. Clean spill area thoroughly with detergent and water.
<b>Clean up - large spill</b>	Review Section 3, 8 and 12 before proceeding with clean up. Use appropriate containment to avoid environmental contamination. Scoop or shovel spilled material into a labeled container for disposal. Avoid creating airborne dust. Close container and move it to a secure holding area.

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**SECTION 6 - ACCIDENTAL RELEASE MEASURES continued**

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**SECTION 7 - HANDLING AND STORAGE**

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<b>General handling</b>	Do not generate airborne dust or expose to ignition sources. Ground and bond all bulk transfer equipment. Keep away from heat. Use with adequate ventilation. Avoid contact with eyes, skin and clothing. Avoid breathing dust. When handling, use proper personal protective equipment specified in Section 8.
<b>Storage</b>	Keep container tightly closed when not in use. Store out of direct sunlight in a well ventilated area at ambient temperature.
<b>Temperature range</b>	15 - 30 °C

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**SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION**

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<b>Exposure limits</b>	<b>Hazardous Ingredient</b>	<b>OEL</b>	<b>Type</b>	<b>Value</b>
	Betaine hydrochloride	Pfizer	TWA-8	Not established
	Oxytetracycline hydrochloride	Pfizer	TWA-8	0.5 mg/m <sup>3</sup>
	Sucrose	ACGIH	TWA-8	10 mg/m <sup>3</sup>
		OSHA	TWA-8	15 mg/m <sup>3</sup> (total dust)
		OSHA	TWA-8	5 mg/m <sup>3</sup> (respirable fraction)
<b>Exposure information</b>	See exposure limits for components listed above.			
<b>Measurement method</b>	Oxytetracycline: CAM-KAS-99-003 (contact Pfizer for additional details).			
<b>Ventilation</b>	Keep airborne contamination levels below the Exposure Limits listed above in this section. General room ventilation is adequate unless the process generates dust or fumes. Do not use in a confined space.			
<b>Eye protection</b>	Safety glasses or goggles.			
<b>Skin protection</b>	Use protective clothing (uniforms, lab coats, disposable coveralls, etc.) in both production and laboratory areas.			
<b>Hand protection</b>	Rubber gloves are recommended if there is a potential for contact.			
<b>Respiratory protection</b>	If the applicable Occupational Exposure Limit (OEL) is exceeded, wear an appropriate respirator with a protection factor sufficient to control exposures to below the OEL.			

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**SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES**

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<b>Physical form</b>	Powder
<b>Color</b>	Yellow
<b>Molecular weight</b>	Not applicable
<b>Molecular formula</b>	Not applicable
<b>pH</b>	Not applicable
<b>Melting point</b>	Not applicable
<b>Pour point</b>	Not applicable
<b>Vapor pressure</b>	Not applicable
<b>Water solubility</b>	No data available
<b>Solvent solubility</b>	No data available

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**SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES** continued

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**SECTION 10 - STABILITY AND REACTIVITY**

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<b>Reactivity</b>	Stable
<b>Conditions to avoid</b>	Contact with moist air causes darkening of this material. Avoid direct sunlight, excessive heat, sparks or open flame
<b>Incompatibilities</b>	Alkalies
<b>Hazardous decomposition products</b>	Exposure to high temperatures may cause decomposition of the active ingredient.
<b>Hazardous polymerization</b>	Will not occur
<b>Oxidizing properties</b>	No data available
<b>Explosive properties</b>	Possible dust explosion hazard (has not been evaluated)

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**SECTION 11 - TOXICOLOGY INFORMATION**

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<b>Acute toxicity</b>	<u>Type</u>	<u>Route</u>	<u>Species</u>	<u>Dosage</u>
	LD50	Oral	Mouse	6696 mg/kg
	LD50	SC	Mouse	600 mg/kg
	LD50	SC	Rat	800 mg/kg
<b>Eye</b>	No data available, see Section 3 - HAZARD IDENTIFICATION, above.			
<b>Skin</b>	No data available, see Section 3 - HAZARD IDENTIFICATION, above.			
<b>Inhalation</b>	No data available, see Section 3 - HAZARD IDENTIFICATION, above.			
<b>Ingestion</b>	Acute oral LD50s for the active ingredient(s) are listed above in the table. While this formulation has not been tested as a whole, it would not be expected to be acutely toxic by ingestion based on the amount of the active ingredient(s) in the mixture.			
<b>Mutagenicity</b>	No evidence of mutagenicity was observed in the Ames test using Salmonella typhimurium strains in the presence or absence of metabolic activation. Oxytetracycline hydrochloride was mutagenic in mouse lymphoma cells L5178Y/TK in the presence but not in the absence of metabolic activation. It was weakly positive in inducing sister chromatid exchanges in cultured Chinese hamster ovary cells with and without metabolic activation but did not induce chromosomal aberrations.			
<b>Subchronic effects</b>	Subacute and subchronic toxicity studies of oxytetracycline hydrochloride were performed in mice and rats for 14 days and 13 weeks. In the 14-day studies, no compound-related gross pathologic effects were seen in mice or rats given up to 100,000 ppm in their feed. In the 13-week studies, no compound-related gross or histopathologic effects were observed in male or female mice or in female rats given up 50,000 ppm in their diet. In male rats, fatty metamorphosis of minimal severity was observed in the liver in all treated animals.			
<b>Chronic toxicity</b>	See Chronic effects/Carcinogenicity below.			
<b>Chronic effects/ Carcinogenicity</b>	Long-term oral chronic and carcinogenicity studies of oxytetracycline hydrochloride toxicity were conducted by the US National Toxicology Program (NTP) in mice at dose levels of 650 or 1400 mg/kg/day and in rats at dose levels of 1000 or 2000 mg/kg/day for 2 years. In mice, no compound-related increases in nonneoplastic or neoplastic lesions were observed in males or females. In rats, increased incidences of pheochromocytomas of the adrenal gland in males and adenomas of the pituitary gland in females were observed. Under the conditions of these 2-year studies, the US National Toxicology Program concluded that there was equivocal evidence of carcinogenicity in male			

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**SECTION 11 - TOXICOLOGY INFORMATION continued**

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	and female rats but no evidence of carcinogenicity in male or female mice.
<b>OSHA carcinogen</b>	No
<b>NTP carcinogen</b>	Not classified
<b>IARC carcinogen</b>	Not classified
<b>Reproductive effects</b>	Effects on fertility (litter size) and embryo- or fetotoxicity were observed in rats at subcutaneous dose of oxytetracycline at 1000 mg/kg, rabbits at intramuscular dose of 789 mg/kg, and dogs (643 mg/kg) (no other details reported). Tetracyclines as a class are capable of crossing the placenta and causing staining of the primary teeth.
<b>Teratogenicity</b>	No increase in congenital defects was found in mice and rats treated with oxytetracycline at oral doses of 1500 and 2100 mg/kg on days 6 - 15 of gestation, respectively. In rabbits, oxytetracycline was administered intramuscularly at 41.5 mg/kg/day from days 10 to 28 of gestation. The number and percentage of partial and total resorptions were significantly increased; no effects on fetal body weight were observed. No abnormalities were found at necropsy.
<b>At increased risk from exposure</b>	Individuals who have shown hypersensitivity to this material or other materials in its chemical class and individuals with liver and/or kidney dysfunction or impairment may be more susceptible to toxicity in cases of overexposure. Individuals with alcoholic liver disease and also individuals with hyperlipidemia, especially hypertriglyceridemia, may be more likely to exhibit fatty changes from tetracycline.
<b>Additional data</b>	PREGNANCY RISK CATEGORY D. Results of animal studies indicate that tetracyclines as a class cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. Tetracyclines as a class are also known to cause tooth discoloration in young children and children exposed to the drug in utero.

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**SECTION 12 - ECOLOGICAL INFORMATION**

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<b>Environmental overview</b>	See Aquatic toxicity data of the active ingredient below:						
<b>Aquatic toxicity</b>	<table><thead><tr><th><u>Type</u></th><th><u>Species</u></th><th><u>Dosage</u></th></tr></thead><tbody><tr><td>LC50/96h</td><td>Lake trout</td><td>&lt; 200 mg/L</td></tr></tbody></table>	<u>Type</u>	<u>Species</u>	<u>Dosage</u>	LC50/96h	Lake trout	< 200 mg/L
<u>Type</u>	<u>Species</u>	<u>Dosage</u>					
LC50/96h	Lake trout	< 200 mg/L					

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**SECTION 13 - DISPOSAL INFORMATION**

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<b>Disposal procedure</b>	Incineration is the recommended means of disposal for this material. This material may also be disposed in landfills. Federal, State and Local environmental regulations and Site conditions may affect proper disposal options.
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**SECTION 14 - TRANSPORTATION INFORMATION**

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<b>Proper shipping name</b>	TERRAMYCIN-343® soluble powder blend
<b>General shipping instructions</b>	Non-regulated

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**SECTION 15 - REGULATORY INFORMATION**

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**EEC Classification/Labelling**

	TOXIC; T
	Substance Toxic to Reproduction; Category 1 (T)
<b>Risk phrases</b>	R61 - May cause harm to the unborn child.
<b>Safety phrases</b>	S53 - Avoid exposure - obtain special instructions before use.
<b>TSCA status</b>	No
<b>SARA section 302</b>	No
<b>SARA section 313</b>	No
<b>California proposition 65</b>	Y (see below)

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**SECTION 16 - OTHER**

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<b>Summary</b>	THIS PRODUCT IS OR CONTAINS CHEMICAL(S) KNOWN TO THE STATE OF CALIFORNIA TO CAUSE DEVELOPMENTAL TOXICITY.
<b>Disclaimer</b>	Pfizer Inc believes that the information contained in this Material Safety Data Sheet is accurate, and while it is provided in good faith, it is without a warranty of any kind, expressed or implied.