DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

I-011741-O-0005-OT

SEP 09 2009

U.S. Department of the Interior
Fish and Wildlife Service
Aquatic Animal Drug Approval Partnership Program
Attention: David Erdahl, PhD
Branch Chief, AADAP
4050 Bridger Canyon Road
Bozeman, MT 59715

Re: Food-use authorization for fish treated with AQUI-S E (eugenol)

Dear Dr. Erdahl:

You are authorized 15 million fish for human and animal food use. Edible tissues derived from experimental animals treated under the conditions described in this letter may be marketed for human consumption, for use in animal feeds, or released into public waters for possible human consumption. Please note the restrictions on the authorization in the authorization table and the text below the table. This authorization is in response to your submission dated May 29, 2009. This authorization for the use of AQUI-S E (eugenol) immersion in fish is consistent with the public health. A separate letter will address additional comments on the protocol included with the submission.

FOOD-USE AUTHORIZATION

DRUG IDENTITY/FEED INGREDIENT IDENTITY	AQUI-S E (50% eugenol)
Dosage Form	Liquid
SPECIES	Fish
Class	All freshwater-reared finfish Freshwater prawn Saltwater fish as listed in Appendix VIa
Number of Animals	15 million
PERMITTED DOSING REGIMEN Maximum Dose (or range)	10 to 100 mg eugenol/L
Route of Administration	Immersion
Frequency and Duration of Dosing	Up to 15 minutes exposure

MINIMUM INVESTIGATIONAL WITHDRAWAL PERIOD	72 hours
MINIMUM INVESTIGATIONAL MILK DISCARD TIME	Not applicable
OTHER RESTRICTIONS OR CONDITIONS	Fish that are illegal for harvest during that 72 hour period can be released immediately after treatment. Euthanized fish must not be sent to slaughter or be otherwise available for food.

CVM noted that one of the primary parameters (i.e., endpoint) in the protocol included euthanasia. Euthanized fish must not be sent for slaughter or be otherwise available for food. Please update your protocol with the statement "Euthanized fish must not be sent to slaughter or be otherwise available for food" in the following locations: Section XII under Euthanized, Section XV, Form AQSE-W, Form AQSE-1, and Form AQSE-3. The revised protocol should be submitted with the annual report.

Section XV (Disposition of Investigational Animals) of the protocol, states that "No withdrawal period will be required for…2) fish that are marked (i.e., tagged) with an easily visible external tag that includes clearly legible words 'Not for Human Consumption'." At this time, CVM is not authorizing the immediate release of tagged fish prior to the completion of the withdrawal period. Please remove the statement after (2) in the second paragraph of Section XV, from the protocol. Please provide additional information that includes type of tag, species and class (size) of fish to be tagged, geographical location where fish will be released, and number of fish expected to be tagged. When this information is submitted, CVM will evaluate the request and determine if tagged fish can be immediately released.

The New Animal Drug Regulations, 21 CFR 511.1(b)(4), require the sponsor to submit specific information prior to each shipment or other delivery of the drug for clinical investigation in animals. The agency has devised a form, Form FDA 3458 (Notice of Claimed Investigational Exemption), which you may use to report shipments for clinical trials. The form and instructions for electronic submission are available on the Center for Veterinary Medicine (CVM) website at http://www.fda.gov/cvm/esubstoc.html. You may file the notice of the drug shipment electronically to CVM. Alternatively, you can send three copies of the completed form to CVM.

This food-use authorization only applies to the treatment regimen stated above. Any change in the dosage regimen or the combining of this treatment with any other drug will require a separate food-use authorization. Drugs given to control animals must be administered in full compliance with the currently approved use. Your investigators should be made aware of their responsibilities under 21 CFR 511.1(b)(7)(ii) and (c)(1).

Clinical tests conducted under the provisions of this letter do not exempt investigational animals and their products from compliance with any other applicable inspection requirements (see 21 CFR 511.1(b)(5)(iii)).

INVESTIGATIONAL LABELING

You provided intended investigational labeling language to be included in the file. This labeling is consistent with the requirements set forth in 21 CFR 511.1(b)(1). The investigational labeling should be affixed to your investigational drug product prior to shipment and this investigational label should be affixed to each individual drug container.

COUNTING NUMBERS OF FISH

You should note that this authorization is for a specific number of fish. Please provide the total number of fish used towards this authorization in your annual reports. We remind you that a fish treated more than once still only counts as a single fish toward the authorization.

Additional numbers of fish may be requested in the future. A request for additional fish should be made with sufficient lead time to allow us to process an amended authorization.

ANNUAL REPORTS

We remind you of the continued necessity to provide annual reports under the FDA/CVM Aquaculture Workload Plan. Your annual report should include: a) a brief summary of the past year's activities and accomplishments in each of the INAD technical sections; b) certification of accountability of all drugs shipped under the INAD, records maintenance for FDA inspection, and compliance with the provisions of 21 CFR Part 511, including notification of adverse effects relative to humans, target animals, or the environment resulting from the use of the investigational drug; c) a list of all investigators, facilities, and species treated; and d) a copy of the current study protocol(s) noting any modification or revision. We recommend that any changes to pivotal study protocols be reviewed by CVM prior to initiating further investigations.

ADDITIONAL COMMENTS

1. In order for us to complete our files, the disposition of all investigational animals and unused drugs should be reported to this office, as well as adverse reactions observed. Please refer to this letter by date and INAD number when reporting the details of clinical investigations or the disposition of investigational animals.

2. We remind you that the investigational new animal drug must be manufactured, processed, packaged, and labeled in such a way as to maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to investigations made with the drug (21 CFR Parts 210 and 211).

3. We note that your submission included a request for a categorical exclusion from the requirement to prepare an environmental assessment. Please note that this letter only addresses the food-use authorization request. Your request for a categorical exclusion will be addressed in a separate letter (X-0006). In the future, please make only one request per submission.

If you submit correspondence relating to this letter, your correspondence should reference the date and the principal submission identifier found at the top of this letter. If you have any questions or comments, please contact Dr. Cindy Burnsteel, Director, Division of Therapeutic Drugs for Food Animals at 240-276-8341.

Sincerely,

Kevin J. Greenlees for

Steven D. Vaughn, DVM
Office of New Animal Drug Evaluation
Center for Veterinary Medicine

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Attention: David Erdahl, PhD
Branch Chief, AADAP
4050 Bridger Canyon Road
Bozeman, MT 59715

Re: Additional comments on protocol included with food-use authorization

Dear Dr. Erdahl:

We refer to your submission dated May 29, 2009, that requests a food-use authorization for use of eugenol for anesthetizing freshwater and marine finfish. The letter provides comments on the protocol included with your submission. A separate letter will describe the details of your food-use authorization for INAD 011741.

CVM recognizes that the submitted protocol is intended for non-pivotal investigations. While we did not review the protocol as a protocol for pivotal studies, we offer the following general comments for non-pivotal investigations and for the assistance in the development of a pivotal protocol. In addition, the changes are suggested to help collect supporting data during non-pivotal investigations that may be used to support a new animal drug application (NADA).

We have the following comments:

1. Section XI of the protocol states "treatment to facilitate fin-clipping would likely require light sedation and a relatively short treatment duration (1-5 minutes), whereas treatment to facilitate implantation of radio transmitters would likely require heavy sedation and a relatively long treatment duration (5-10 minutes)." However, Section XII describes the Primary Treatment Response Parameters as including "handleable", "anesthetized", "euthanized", and "recovered." The term "anesthesia," as defined in Section XII, may be more appropriate than "deep sedation" for procedures such as radio transmitter implantation. We recommend that terminology be consistent throughout the protocol for clarity.

2. Please update the protocol and data capture forms, where applicable, to reflect the correct withdrawal period, the date of the CVM authorization letter, and include the statement "Euthanized fish must not be sent to slaughter or be otherwise available for food."

3. On Form AQSE-3, please change the header on column five to AQUI-S E. Page 3 of the Form asks if the treatment was successful, but the protocol does not define what treatment success is (i.e., no mortalities, all fish become sedated and recovered within desired time period, etc.). Please define treatment success. CVM also suggests that the definitions of handleable, anesthetized, euthanized, and recovered be included on the form so they are easy for the investigators to find.

If you submit correspondence relating to this letter, your correspondence should reference the date and the principal submission identifier found at the top of this letter. If you have any questions or comments, please contact me at 240-276-8341. You may also contact Dr. Jennifer Matysczak, Leader, Aquaculture Drugs Team, at 240-276-8338.

Sincerely,

Cindy L. Burnsteel DVM

Cindy L. Burnsteel, DVM
Director, Division of Therapeutic
Drugs for Food Animals
Office of New Animal Drug Evaluation
Center for Veterinary Medicine