



I-011236-D-0031-OT

DEC 20 2007

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

Re: Request for amended authorization for 17 α -methyltestosterone medicated feed

Dear Dr. Erdahl:

You are authorized to slaughter 30 million tilapia to market for human food use the edible tissues derived from experimental animals treated as described in this letter. The use of 17 α -methyltestosterone (17MT) administered as a medicated feed as described in your August 24, 2007, submission is consistent with the public health.

AMENDED AUTHORIZATION

DRUG	17 α -methyltestosterone
Dosage Form	Type C medicated feed
Route of Administration	Oral
SPECIES	Tilapia as described in Appendix VIa of this submission
Class	Fry
Number of Animals	30 million tilapia
MAXIMUM DOSE (or Range) Frequency and Duration	60 mg 17MT/kg feed for 28 days
MINIMUM WITHDRAWAL PERIOD	120 days or a minimum body weight of 350 grams
RENDERING	Fish may not be rendered prior to completing the investigational withdrawal period or reaching the minimum body weight.
Other Restrictions	None
Reference to other authorizations	All previous authorizations are superseded

Clinical investigations for this INAD cover only the treatment regimen stated above. The combining of this treatment with any other drug will require a separate 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 sections 511.1(b)(7)(ii) and 511.1(c)(1) of the new animal drug regulations.

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.

In order for us to complete our files, the disposition of all investigational animals and unused drug must 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.

ENVIRONMENTAL CONSIDERATIONS

We find your claim for an extension of investigational use of 17MT for gender manipulation in tilapia falls within the categorical exclusion in 21 CFR 25.33(e), subject to the reporting and effluent discharge limitations described below. Your submission states that, to your knowledge, no extraordinary circumstances exist which may significantly affect the human environment. Therefore, neither an environmental assessment (EA) nor an environmental impact statement (EIS) is required. This categorical exclusion from the preparation of an EA and EIS does not relieve you of the responsibility for determining and meeting all Federal, State, and local environmental and occupational laws and regulations that apply to the manufacturing, use, and disposal of the investigational drug.

You and your site investigators remain responsible for complying with the Federal Clean Water Act as implemented under the National Pollutant Discharge Elimination System (NPDES), as well as any applicable groundwater pollution requirements. For all investigational sites covered under this INAD, site investigators must report INAD use of 17MT to the permitting authority authorized to administer the NPDES permitting program for the receiving waters into which a facility discharges (see 40 CFR 451.3(a)).

As previously described in our letter to you dated June 4, 2004 (A-0000), we have concerns for the introduction of 17MT into surface and groundwater because it is physiologically active at concentrations $<1 \mu\text{g/L}$ (ppb). The results of recently published fish toxicology studies on 17MT have confirmed and heightened these concerns. As a result, it is necessary to continue to limit the environmental introduction (i.e., effluent discharge) of this compound from all investigational uses to less than 1 ppb. This should insure for sufficient dilution in receiving water to reduce the concentration below the level of concern. Procedures should be implemented in your studies to assure that this limitation is met at all facilities. With this limitation, the investigational uses can continue to be categorically excluded.

If you cannot assure that concentrations $<1 \mu\text{g/L}$ of 17MT will be released in effluents or leached to groundwater, an environmental assessment (EA) must be submitted which specifically addresses possible environmental impacts arising from the proposed uses described in the amended authorization request.

If additional information on the fate or effects of 17MT becomes available, it may be necessary to modify the effluent limitation for 17MT and/or require testing as part of the INAD or in preparation for a new animal drug application (NADA).

If the scope of the investigations changes (e.g., additional facilities or indications are added) potentially resulting in increased use and/or environmental release of 17MT, we request that you submit either a revised statement for categorical exclusion as described in 21 CFR 25.15(d) or an EA under 21 CFR 25.40 for the expanded use.

We ask you to contact Dr. Eric Silberhorn of the Environmental Safety Team to discuss collection and submittal of appropriate information from the individual site investigators on the potential use and release of 17MT from these facilities, including information on the feasibility of no discharge. This information is necessary in order for CVM to determine environmental introduction concentrations for 17MT, data which are needed to make decisions in the future on any additional authorization requests for 17MT. This information will also need to be included in any EA that will be prepared to support a NADA approval of this drug in the future.

INVESTIGATIONAL LABELING

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.

The investigational labeling, as provided in your August 24, 2007, submission, should be affixed to your investigational drug product prior to shipment for studies conducted under 21 CFR 511.1(a) or (b), as appropriate. The investigational labeling should be affixed to each individual drug container.

SHIPMENT AND DELIVERY NOTIFICATION

The new animal drug regulations, sections 511.1(b)(3) and (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), which you as the sponsor may use to report shipments for clinical trials. You may file the notice of the drug shipment electronically to CVM. Please refer to the Center's electronic submission information on the CVM website at <http://www.fda.gov/cvm/esubstoc.html>.

You must maintain records of dates, amount of drug received in each shipment, and batch or code mark of each shipment for a period of 2 years after such shipment and delivery. These records should be made available for inspection and copying upon our request.

COUNTING NUMBERS OF FISH

You should note that this authorization is for a specific number of fish. You should begin counting the number of animals used from the date you receive our letter starting at zero.

Previous authorizations are superseded. In the future, it would be helpful if you would supply the total number of animals used along with your annual reports.

Having a specific number of animals, rather than annual numbers, facilitates our tracking of fish numbers under the INAD. We remind you that a fish treated more than once still only counts as a single animal toward the authorization.

ANNUAL REPORTS

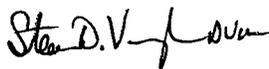
We remind you of the continued necessity to provide annual reports under the FDA/CVM Aquaculture Workload Plan. Your annual report should comprise: a) a brief summary of the past year's activities and accomplishments in each of the technical sections for the NADA; b) certification of accountability of all drugs shipped under the INAD, records maintenance for FDA inspection, 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

You requested that 70 million fish be granted for this amended authorization. We are granting authorization for 30 million fish due to ongoing concerns regarding potential discharges of 17MT from facilities using the investigational drug. We estimate that the 30 million fish would be used over a 1 ½ year period, which should provide sufficient time to collect and submit the information requested in the "Environmental Considerations" section above. This information should better delineate current discharge practices of facilities using or likely to use 17MT under the INAD.

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. Joan C. Gotthardt, Director, Division of Therapeutic Drugs for Food Animals, at 301-827-7571.

Sincerely,



Steven D. Vaughn, DVM

Director

Office of New Animal Drug Evaluation
Center for Veterinary Medicine