



Food and Drug Administration  
Rockville MD 20857

I-011375-A-0000

U.S. Department of 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

DEC 1 5 2005

Re: Request to establish an Investigational New Animal Drug (INAD) file and request for a categorical exclusion.

Dear Dr. Erdahl:

We have reviewed your submission dated May 9, 2005. For administrative purposes, we have assigned your file number INAD 011375 for the use of salmon gonadotropin releasing hormone analogue (OVAPLANT) in finfish. Please refer to this number in all drug shipments and correspondence concerning the drug while it is in investigational use.

#### AUTHORIZATION FOR THE USE OF EDIBLE PRODUCTS

This letter does not authorize the use of edible products derived from animals treated with your investigational drug. In accordance with 21 CFR 511.1(b)(5), you must request and be granted an authorization for slaughter from CVM before you can use the edible tissues from investigational animals treated with your unapproved drug. When you request a slaughter authorization for treated animals, the request should be in writing and should include the following information: species, age, and class; proposed maximum dose and duration of treatment; method of administration; preliminary toxicological and metabolic data; and a Material Data Safety Sheet. You may also propose the number of animals to be covered by the authorization and a suggested withdrawal time.

#### INVESTIGATIONAL LABELING

You submitted a copy of the intended investigational labeling to be included in the file. This labeling is consistent with the requirements set forth in CFR 511.1(b). 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.

#### NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION

The new animal drug regulations, Section 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 which you as the sponsor may use to report shipments for clinical trials. Three copies of the completed Notice of Claimed

Investigational Exemption (NCIE) form should be submitted for each trial. Alternatively, 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.

#### ENVIRONMENTAL CONSIDERATIONS

We have reviewed the information provided in your submission on the proposed use of OVAPLANT (produced by Syndel International) containing a salmon gonadotropin releasing hormone analogue (sGnRHa) to induce final gamete maturation in a variety of fish species under an INAD exemption. It is our understanding that as many as 20,000 fish of 43 different species may be treated with OVAPLANT under the INAD. The submitted Study Protocol identifies potential use under the INAD at 32 aquaculture facilities in 21 states, although additional facilities will likely choose to participate. Each fish will be injected with OVAPLANT pellets containing 75, 150, or 250 µg of sGnRHa. All treated fish will be maintained in culture facilities indefinitely or destroyed.

Quantitative information is lacking on the potential release of sGnRHa to the environment through excretion by treated fish. However, based on the limited amount of sGnRHa expected to be used during these studies and its extended release from OVAPLANT, we believe that the likelihood of significant environmental impacts from the investigation use is low.

We agree with your claim that the investigational use of OVAPLANT (sGnRHa) in finfish falls within the categorical exclusion under 21 CFR 25.33(e). 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 is required. This categorical exclusion from preparation of an EA 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 drugs.

You 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 ground-water pollution requirements. For all investigational sites covered under this INAD, you must contact the offices responsible for issuing NPDES permits, and other similar permits, to be certain they have no objection to the use and release of this investigational drug.

If the scope of the investigations changes (e.g., additional facilities or protocol changes that could result in increased environmental exposure), we request that you submit either a revised statement for categorical exclusion as described in 21 CFR 25.15(d) or an environmental assessment (EA) under 21 CFR 25.40 for the expanded use.

It will be necessary to provide information on the possible impacts of sGnRH $\alpha$  on the environment at the time a new animal drug application (NADA) is submitted for the product. Therefore, it is important to begin gathering information on the possible fate and effects of sGnRH $\alpha$  in the environment from the proposed use. Information on the *in vivo* degradation and/or excretion of sGnRH $\alpha$  would be particularly useful for the environmental assessment. For further information on conducting environmental assessments for veterinary drugs, we refer you to our Guidance for Industry 89 (<http://www.fda.gov/cvm/Guidance/guide89.PDF>) and VICH GL 38 ([http://vich.eudra.org/pdf/10\\_2004/GL38\\_st7.pdf](http://vich.eudra.org/pdf/10_2004/GL38_st7.pdf)).

#### ADDITIONAL COMMENTS

1. 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.
2. In order for us to complete our files, the disposition of all investigational animals and unused drugs 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.
3. CVM encourages you to discuss study design issues and submit protocols to the Center for review prior to initiating pivotal studies. Guidance for developing specific study designs can be found on the CVM webpage.

#### GENERAL COMMENTS

1. You state that OVAPLANT may be administered to 14,540 fish, of up to 43 species, each year. You also state that 20,000 fish will be treated under the INAD. Please clarify the number of fish to which OVAPLANT may be administered each year.
2. You authorized disclosure of the existence of the INAD. Please confirm that disclosure limited to the existence of the INAD is permitted, rather than complete disclosure for the contents of the INAD file, including all study results.

#### PROTOCOL COMMENTS

Overall the protocol was well organized. However, the protocol includes some outdated references and with some revision, the data collected would be more likely to support a new animal drug approval for the use of OVAPLANT in finfish. The protocol should be revised according to the following comments.

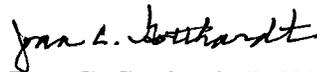
1. The protocol describes the injection site as the dorsal musculature. The description of the injection site should include more detail, such as using anatomic landmarks. The injection site should be consistent amongst the study sites so that any potential differences in drug absorption may be minimized. This type of information will likely be needed on the product label. Please provide additional detail regarding the injection site for the test article.

2. The protocol states that the experimental unit may be either individual fish or groups of fish. Since the study described by the protocol will not always include control fish, and treatments are unlikely to be randomly assigned, the experimental unit should be considered the individual fish whenever possible. This would be easiest if the fish were individually identified. However, data could be collected from individual fish that are arbitrarily identified at the time eggs or milt are collected for the purpose of identifying the spawn and to correlate the secondary variables to the results for the individual male and female fish. Please describe in the protocol the number of times eggs and milt will be collected from each fish. Both the male and female fish should be identified on the data capture forms where the secondary variable data are recorded.
3. The primary variable identified in the protocol is percent "ripe." This is basically a ratio of successful to unsuccessful treatments. This would be calculated based on the results of a group of fish. Since the test article is administered to individual fish and individual fish will be examined to determine treatment results, the primary variable should be based on the observations from individual fish. Also, the protocol does not describe when or how frequently fish will be examined after the implant is administered to determine when the fish are "ripe." The protocol also does not state at what point the fish will be considered treatment failures. A more appropriate primary variable may be successful release of mature gametes by a particular day. The primary variable should directly relate to the label claim.
4. The secondary variables described in the protocol are percent eye-up and percent hatch for the female fish. These are appropriate secondary variables since the development of eggs and the hatch rate may be affected by more factors than the quality of the eggs, such as milt quality and environmental conditions. The protocol should describe how and when these variables will be assessed.
5. Form sGnRHa/Ovaplant-3 provides spaces to record information for either individual fish or for a group of fish. Regardless of the experimental unit included in each study, data should be collected for individual fish with appropriate averages for treatment response variable calculated from the individual observation. The data capture forms should be designed so that data are recorded from individual fish observations rather than recording averages or estimates based on groups of fish.
6. Section ~~VII~~<sup>X</sup> of the protocol describes the actions for an investigator to take when adverse reactions are observed. However, the protocol should include a section or section ~~VII~~ should be revised to refer to all adverse events. An adverse event may or may not be treatment related. Disease outbreaks and changes in water quality, among other things, are examples of adverse events. Information regarding any adverse events occurring during a study should be recorded. Then a determination may be made regarding whether or not the event was treatment-related.
7. The protocol provides no mention of examining fish that have died or are euthanized during the study. All fish that die or are euthanized during the study should undergo complete necropsy that includes examination of the injection site. Necropsy information will provide some target animal safety data.

8. Section IX of the protocol states that sGnRH $\alpha$  (OVAPLANT) qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.24(d)(4). The citation is outdated. The reference to the citation may be eliminated since a request for a categorical exclusion referencing the correct citation was made in the cover letter. Otherwise the statement should be revised to include the correct citation, 21 CFR 25.33(e).
9. Section XVIII of the protocol states that the annual report will probably include a request for an extension of the INAD based on the data collected during that year. CVM no longer renews compassionate INADs annually. The INAD file and investigations under the INAD may continue as long as drug shipment reporting requirements and progress reports of studies are provided to CVM to demonstrate due diligence in generating the data needed for an NADA application. Since protocol section XVIII is entitled "Plans for Data Analysis," the information in the section should relate to the analysis of data, rather than the information included in a study report.

If you submit correspondence relating to this letter, you should reference this letter by date and the principal submission(s) identifier found at the top of this letter. If you have any questions, please contact me at 301-827-7571, or Dr. Donald Prater, Leader, Aquaculture Drugs Team, at 301-827-7567.

Sincerely,



Joan C. Gotthardt, D.V.M.  
Director, Division of Therapeutic  
Drugs for Food Animals  
Office of New Animal Drug Evaluation  
Center for Veterinary Medicine