

FEB 06 2008

I-011669-E-0004-EF

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

Re: Review of effectiveness protocol H2O2-07-EFF.1

Dear Dr. Erdahl:

We concur with the protocol you submitted on December 19, 2007, and amended on January 22, 2008 (I-011669-T-0005). The protocol was entitled "The Efficacy of 35% PEROX-AID (35% hydrogen peroxide) to Control Mortality Due to Bacterial Gill Disease or External Columnaris in Cool and Warmwater Finfish." You submitted this protocol to the investigational new animal drug (INAD) file I-011669 for 35% hydrogen peroxide. 35% hydrogen peroxide is proposed for the control of mortality due to bacterial gill disease and columnaris in freshwater-reared finfish.

Our concurrence means we fundamentally agree with the design, execution, and analyses proposed in your protocol, and represents a commitment that we will not later alter our perspectives on these issues unless public or animal health concerns appear that we did not recognize at the time of the protocol assessment. However, our concurrence with this protocol does not guarantee that the data obtained from a study that implements your protocol will support an approval. Because this concurrence does not extend to any subsequent changes you make to this protocol, you may want to seek our concurrence on the revised protocol if you make changes. When you submit a final study report, please be sure to include a copy of the protocol under which the study was actually conducted, and include any protocol deviations, amendments, and explanations.

We remind you that when you are conducting your studies you should be testing the final formulation of your product.

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 or Dr. Donald Prater, Aquaculture Drugs Team Leader, at 240-276-8343.

Sincerely,

A handwritten signature in black ink that reads "Cindy L. Burnsteel, DVM". The signature is written in a cursive style with a large, stylized initial "C".

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



U.S. Fish & Wildlife Service  
Aquatic Animal Drug Approval Partnership Program



4050 Bridger Canyon Road  
Bozeman, MT 59715

phone: (406) 587-9265 / fax: (406) 582-0242  
[www.fws.gov/fisheries/aadap](http://www.fws.gov/fisheries/aadap)

January 22, 2008

Dr. Joan Gotthardt  
Director, Division of Therapeutic Drugs  
for Food Animals  
Document Control Unit, HFV-199  
Center for Veterinary Medicine  
7500 Standish Place, MPN-2  
Rockville, MD 20855

Dear Dr. Gotthardt:

The purpose of this submission is to provide CVM with amended material for inclusion in, and CVM review of, the pivotal efficacy Study Protocol titled "The Efficacy of 35% PEROX-AID<sup>®</sup> to Control Mortality Due to Bacterial Gill Disease or External Columnaris in Cool and Warmwater Finfish." The enclosed amended Study Protocol is identified by Study Protocol Number H2O2-07-EFF.1 (revision date January 22, 2008). This study protocol was originally submitted to CVM in a letter dated December 19, 2007. The amended study protocol includes revisions to the following sections: (a) Section 1.1 Objective, (b) Section 1.2 Background, (c) Section 2.1.9 Dose(s) to be tested, (d) Section 2.1.11 Distribution site, (e) Section 3.2 Schedule of Events, (f) Section 6.1.4.2 Actual counts, (g) Section 7.3.4 Biostatistical procedures used, and (h) Appendix I. No other sections of the protocol were changed.

Use of 35% PEROX-AID<sup>®</sup> in pivotal field efficacy trials will be conducted under INAD #11-669. Efficacy data generated from these studies will be used to support a new animal drug application for the use of 35% PEROX-AID<sup>®</sup> to control mortality in a variety of freshwater cool- and warmwater finfish. We refer to your INAD file number INAD I-011669-E-0001-EF dated November 13, 2007.

The current sponsor for INAD #11-669 is Dr. David Erdahl, Branch Chief, U.S. Fish and Wildlife Service, AADAP Program, 4050 Bridger Canyon Road, Bozeman, MT 59715. We would like to thank you in advance for your time and consideration with respect to the above described request. If you have questions, please contact Dr. Erdahl at (406)-994-9904.

Sincerely,

Dr. David Erdahl  
Branch Chief, AADAP Program

Enclosure: Three copies of the amended study protocol, H2O2-07-EFF.1 (revision date January 22, 2008)





**U.S. Fish & Wildlife Service  
Aquatic Animal Drug Approval Partnership Program**



4050 Bridger Canyon Road  
Bozeman, MT 59715

phone: (406) 587-9265 / fax: (406) 582-0242  
[www.fws.gov/fisheries/aadap](http://www.fws.gov/fisheries/aadap)

December 19, 2007

Dr. Joan Gotthardt  
Director, Division of Therapeutic Drugs  
for Food Animals  
Document Control Unit, HFV-199  
Center for Veterinary Medicine  
7500 Standish Place, MPN-2  
Rockville, MD 20855

Dear Dr. Gotthardt:

The purpose of this submission is to request a formal review of the enclosed revised pivotal efficacy Study Protocol titled "The Efficacy of 35% PEROX-AID<sup>®</sup> to Control Mortality Due to Bacterial Gill Disease or External Columnaris in Cool and Warmwater Finfish." The Study Protocol is identified by Study Protocol Number H2O2-07-EFF.1. This Study Protocol is a revision of Study Protocol Number H2O2-07-EFF titled "The Efficacy of 35% PEROX-AID<sup>®</sup> to Control Mortality Due to Bacterial Gill Disease or External Columnaris in Cool and Warmwater Finfish" that was submitted to FDA's Center for Veterinary Medicine (CVM) on September 26, 2007. The initial Study Protocol has been revised to address CVM's concerns that were outlined in a letter to the USFWS's AADAP Program dated November 13, 2007 (E-0001-EF). Listed below are the specific AADAP responses to each CVM comment from that letter. We refer to your INAD file number INAD I-011669-E-0001-EF dated November 13, 2007.

**GENERAL COMMENTS**

**Comment 1:** In many places (Sections 1.1, 5.6 (table), and 7.3, and on Form 2), the protocol indicates that hydrogen peroxide will be administered on alternate days. However, Section 3.2.3 of the protocol says that the hydrogen peroxide will be administered on consecutive days. The dosing regimen should be consistent throughout the protocol. Please correct the protocol and forms where necessary.

**AADAP response** – All references to treatment on consecutive days have been changed to indicate that treatments will be administered on alternate days.

**Comment 2:** Section 2.1.8 states that treatments will be administered for up to 60 minutes, whereas the dosing regiment table in Section 5.6 identifies the treatment duration as 60 minutes. Please change Section 2.1.8 so that the treatment duration is 60 minutes. If you are considering evaluating a different treatment duration in some studies, then the exact duration should be specified in both places in the protocol (do not give a range).

**AADAP response** – All references to treatment duration for up to 60 minutes have been changed to indicate that treatment duration will be 60 minutes.

**Comment 3:** Please specify that the person(s) conducting the necropsies will be masked to treatment group (Section 5.5).

**AADAP response** – Section 5.5 has been changed to indicate that blinded study personnel will conduct necropsies.

**Comment 4:** Please remove references to ectoparasites in Section 3.2.4. The protocol discusses secondary disease infections, which includes presence of ectoparasites, in Section 5.3.1.

**AADAP response** – All reference to ectoparasites in Section 3.2.4 have been removed.

**Comment 5:** Section 5.4.3 indicates that either a copy or transcription of facility records capturing mortality data for the days leading up to the study should be submitted in the FSR. A photocopy is acceptable but transcription is not. Please remove the words “or transcription” from this section.

**AADAP response** – All references to transcription of facility records have been removed. Facility data to be included in the Final Study Report will be photocopied.

## **BIOMETRICS COMMENTS**

**Comment 1:** Sections 4.2 and 4.3 indicate that, while a completely randomized design primarily will be used to assign treatment to tanks, other designs may be used when appropriate. However, in Sections 3.2.1 and 4.4 it is stated that a completely randomized design will be used, and there is no mention of the possibility of other designs. CVM requests that the protocol state that other appropriate designs may be used wherever the study design is discussed. For example, the third sentence of Section 3.2.1 can be reworded as (changes in italics), “Allocation of fish-to-tanks will be done following a completely randomized design *or other appropriate design.*”

**AADAP response** – Language describing the study design has been changed to include the statement, “*or other appropriate design.*” This change has been made in Sections 3.2.1 and 4.4.

**Comment 2:** Section 5.5.1 states that sample counting may be done by masked or unmasked personnel. This is acceptable for those doing pre-treatment sample counting. However, those counting fish at the end of post-treatment, regardless of what counting method they use, should be masked to treatment.

**AADAP response** – Blinded or non-blinded study personnel may *sample count* fish before the start of the study. However, blinded study personnel will be responsible for hand-counting or weighing fish out of tanks at the end of the study.

**Comment 3:** Section 6.1.4.1 states that on rare occasions a sample count may be done at the end of post-treatment. However, it does not indicate from which tank(s) the sample of fish will be selected to do the

count. CVM recommends that, if this procedure is used, a sample be selected from each tank and its weight applied to only that tank when estimating the number of fish in the tank.

**AADAP response** – Section 6.1 has been revised to indicate that if fish are weighed out at the end of the study, a sample count will be done for each tank and an average fish weight will be determined for that tank.

**Comment 4:** The last sentence in the “Actual counts at the end of the study” part of Section 6.1.4.2 states, “Results from hand-counting fish from experimental units will be added to the total mortality in each of the test tanks, resulting in an accurate number of fish/test tank at the start of the study.” Please explain the purpose of this statement. It implies that when live fish are hand-counted at the end of the study, the estimated total fish count the start of the study will be replaced with the sum of the mortality count and the live fish hand count.

**AADAP response** – Section 6.1 has been revised to state the total number of fish transferred to each tank at the start of the study will be determined at the end of the study by adding the total mortality in each test tank to the number of live fish in each tank at the end of the study.

**Comment 5:** Assumption 2 in Section 7.3.3 states that the equality of the variances between the two treatment groups is known. The analysis will be done on proportions, and the variance of the mean changes according to the proportion. Therefore, this assumption is not correct. Please remove this assumption from Section 7.3.3.

**AADAP response** – Assumption 2 has been removed from Section 7.3.3.

**Comment 6:** The protocol indicates several times that the tank will be treated as the experimental unit. However, the protocol does not indicate that this will be done in the analysis. We recommend that in Section 7.3.4 the protocol state that tank will be treated as the experimental unit in the analysis. Remember that tank can be treated as the experimental unit in the generalized linear model analysis, for example, in SAS Proc GLIMMIX. To do so, enter the response in the model statement as the ratio of the number of mortalities divided by the total number of fish in the tank.

**AADAP response** – A statement indicating that the test tank will be treated as the experimental unit in the analysis has been added to Section 7.3.4.

**Comment 7:** In the generalized linear model analysis, the mean square error should be multiplied by the overdispersion parameter. This can be done, for example, in SAS Proc GLIMMIX by including a “random residual” statement. Please indicate in Section 7.3.4 that in the analysis the mean square error will be multiplied by the overdispersion parameter.

**AADAP response** – The following sentence was added to Section 7.3.4, “In the analysis, the mean square error will be multiplied by the overdispersion parameter.”

## **ADDITIONAL COMMENTS**

**Comment 1:** In Section 3.3, the protocol provides a table with the number of studies to be conducted. We agree that this reflects the minimum number of studies needed to supplement data from the United States Geological Survey Upper Midwest Environmental Sciences Center (UMESC) to complete the effectiveness technical sections for control of mortality in coolwater species of freshwater-reared finfish due to bacterial gill disease and in warmwater species of freshwater-reared finfish due to external

columnaris. The table in the protocol indicates that you will conduct one pivotal and one supportive study in any coolwater species; you should use a different species in each study. For the warmwater species, CVM encouraged UMESC to select a species that is commonly raised in aquaculture facilities in the United States such as hybrid striped bass. Depending on doses used for certain species or lifestages, additional target animal safety data may be required.

**AADAP response** – A footnote has been added to the table stating “effectiveness studies will be conducted on different coolwater fish species”.

**Comment 2:** You protocol defines the causative agent of bacterial gill disease to genus (*Flavobacterium spp.*) If you wish for the indication to match that which is currently approved for freshwater-reared salmonids, “control of mortality...due to bacterial gill disease associated with *Flavobacterium branchiophilum*,” then your studies will need to confirm the presence of this species of bacteria.

**AADAP response** – Based on a phone conversation on December 12, 2007 with some of CVM’s Aquaculture Drugs Team (Dr. Don Prater, Dr. Jen Matysczak, and Dr. Matt Lucia), we revised the protocol to refer to causative agent of bacterial gill disease as “infectious fish pathogens such as *Flavobacterium branchiophilum*.” The phone conversation was arranged to discuss the difficulty of culturing *F. branchiophilum* and our concern that successful effectiveness studies may be invalidated due to failure to make a definitive confirmation of the pathogen. CVM’s Aquaculture Drugs Team has been struggling with this issue and recommended we use the language that has been included in the protocol.

**Comment 3:** The proposed method of disease diagnosis is acceptable for this protocol, but definitive diagnosis (for instance, by bacterial culture) using at least a subset of samples is preferable.

**AADAP response** – See the AADAP response to the above comment. We will make a good faith effort to culture and confirm diagnosis of the pathogen causing fish mortality in studies conducted under this protocol.

**Comment 4:** Section 1.2 of the protocol says that the manufacturing sponsor would ultimately like the label indication for 35% PEROX-AID® to be “use as an external microbicide for all freshwater-reared finfish eggs and freshwater-reared finfish.” We remind you that CVM approves claim for specific diseases and etiological agents for which there is substantial evidence that the drug is effective in controlling or treating the disease or controlling mortality due to the disease. For a claim as an “external microbicide,” a sponsor would need to demonstrate that the drug is effective against all microorganisms that can potentially cause disease in fish.

**AADAP response** – This section has been rewritten to include the statement that the manufacturing sponsor would like the label claim of 35% PEROX-AID® to read “Use to control mortality of all freshwater-reared finfish caused by Bacterial Gill Disease caused by infectious fish pathogens such as *F. branchiophilum* and external columnaris caused by *F. columnare*.”

**Comment 5:** Fourteen days is an acceptable length for a post-treatment period without re-infection. In certain circumstances, a post-treatment period between 10 and 14 days may be acceptable. If you analyze data at 10 days post-treatment as described in Section 3.2.4, you will need to provide an adequate and acceptable justification for the decision to shorten the post-treatment in the final study report.

**AADAP response** – Section 3.2.4 has been changed to state the post-treatment period will last at least 14 d. Ideally, the post-treatment period will be terminated after 14 d. However, on occasion, the end of the post-treatment period may land on a weekend or holiday. Therefore, we propose to extend the post-treatment period until the next work day.

**Comment 6:** Section 4.4 states that all completely randomized design procedures will follow SOP MISC 327 in Appendix E. We believe that you intended to reference SOP MISC 237. Please correct this typographical error.

**AADAP response** – This typographical error has been fixed.

**Comment 7:** In Section 5.1.2.2, to avoid confusion, please indicate who will calculate the loading rate. Currently, the protocol says “we will mathematically calculate...” and is therefore ambiguous.

**AADAP response** – In Section 5.1.2.2, “we” has been replaced with “the OSI, SD or their designee.”

**Comment 8:** Section 5.7 indicates that subjects will be removed from experimental units using dip nets that are sanitized before and after use with disinfectant. Please provide more instruction on the disinfection step to ensure that disinfectant does not contaminate the water in the experimental units and contribute to target animal toxicity. For instance, an acceptable explanation would be that the nets will be rinsed with water before use.

**AADAP response** – Sentence has been added to Section 5.7 stating that all nets will be rinsed in freshwater before use in test tanks.

**Comment 9:** In Section 5.9.3, the protocol states that if it is not possible to measure hardness, alkalinity, or pH, that it will be acceptable to report historical data. Water quality parameters should be measured during the study.

**AADAP response** – Section 5.9.3 has been rewritten to indicate that we will measure hardness, alkalinity, and pH for each study.

**Comment 10:** There is no place on Form 1 or other forms to record the water temperature and DO of the reference population tank. Since the protocol calls for this measurement, there should be a place on one of the forms for this information, unless it will be documented in facility records that will be copied for inclusion in the final study report.

**AADAP response** – Form 1 has been revised by adding an area for documenting temperature and DO in the reference population tank.

**Comment 11:** It would also be appropriate to have a place on Form 1 to report the frequency and number of treatment administrations.

**AADAP response** – Form 1 has been revised by adding an area for documenting the frequency and number of treatment administrations.

**Comment 12:** In your correspondence to us dated October 9, 2007, you indicated that the use of 35% PEROX-AID® under INAD 011669 for the control of mortality caused by BGD and external columnaris would be limited to use at a single facility (Richloam State Hatchery, FL) on a limited number of species. The current protocol is not specific for Richloam State Hatchery and the species listed in your correspondence dated October 9, 2007. Should you wish to conduct studies at other facilities on additional species, please request a categorical exclusion for these facilities and be sure that the species fall under your authorization. We are in the process of evaluating your request for a slaughter authorization dated September 6, 2007, and amendment dated October 9, 2007.

**AADAP response** – Should we conduct studies at facilities other than Richloam Fish Hatchery or on fish species not described in the protocol; a categorical exclusion will be requested.

**Comment 13:** Section 13 of the protocol says that unused drug remaining at the end of a study can be kept on-site for future use according to the Service's Study Protocol for Compassionate Aquaculture INAD Exemption under INAD 011669. We have not received a compassionate protocol for BGD and columnaris from you for this INAD. You indicated in your correspondence dated October 9, 2007, that use of the drug under this INAD for control of mortality due to BGD and columnaris would be pivotal in nature. Additionally, your previous correspondence indicates that bacterial and ectoparasite trials will be done at separate facilities. This section of the protocol should not say that the drug will be used in compassionate studies if there is to be no such use of this drug in that manner. Similarly, please remove reference to compassionate protocol use in Section 5.2.1.

**AADAP response** – References to the compassionate INAD protocol in sections 13 and 5.2.1 have been removed.

The current sponsor of INAD #11-669 is Dr. David Erdahl, Branch Chief, Aquatic Animal Drug Approval Partnership (AADAP) Program, U.S. Fish and Wildlife Service, 4050 Bridger Canyon Road, Bozeman, MT. We would like to thank you in advance for your time and consideration with respect to the above-described request. If you have any questions, please contact Dr. Erdahl at (406) 994-9904.

Sincerely,



Dr. David Erdahl  
Branch Chief, AADAP Program

Enclosure: 3 copies of revised Study Protocol Number H2O2-07-EFF.1



NOV 13 2007

I-011669-E-0001-EF

U.S. Fish & Wildlife Service  
Aquatic Animal Drug Approval Partnership Program  
Attention: David Erdahl  
Branch Chief  
4050 Bridger Canyon Road  
Bozeman, MT 59715

Re: Review of effectiveness protocol H202-07-EFF

Dear Dr. Erdahl:

We do not concur with the protocol you submitted on September 26, 2007. This protocol was entitled "The efficacy of 35% PEROX-AID to control mortality due to bacterial gill disease or external columnaris in cool and warmwater fish." You submitted this protocol to the investigational new animal drug (INAD) file I-011669 for hydrogen peroxide. Hydrogen peroxide is proposed for the control of mortality in freshwater-reared finfish due to bacterial gill disease and external columnaris. We found the protocol unacceptable for the following reasons:

#### GENERAL COMMENTS FOR PROTOCOL CONCURRENCE

1. In many places (Sections 1.1, 5.6 (table), and 7.3, and on Form 2), the protocol indicates that hydrogen peroxide will be administered on alternate days. However, Section 3.2.3 of the protocol says that the hydrogen peroxide will be administered on consecutive days. The dosing regimen should be consistent throughout the protocol. Please correct the protocol and forms where necessary.
2. Section 2.1.8 says that treatments will be administered for up to 60 minutes, whereas the dosing regimen table in Section 5.6 identifies the treatment duration as 60 minutes. Please change Section 2.1.8 so that the treatment duration is 60 minutes. If you are considering evaluating a different treatment duration in some studies, then the exact duration should be specified in both places in the protocol (do not give a range).
3. Please specify that the person(s) conducting the necropsies will be masked to treatment group (Section 5.5).
4. Please remove references to ectoparasites in Section 3.2.4. The protocol discusses secondary disease infections, which includes presence of ectoparasites, in Section 5.3.1.
5. Section 5.4.3 indicates that either a copy or transcription of facility records capturing mortality data for the days leading up to the study should be submitted in the FSR. A

photocopy is acceptable but transcription is not. Please remove the words "or transcription" from this section.

#### BIOMETRICS COMMENTS

1. Sections 4.2 and 4.3 indicate that, while a completely randomized design primarily will be used to assign treatments to tanks, other designs may be used when appropriate. However, in Sections 3.2.1 and 4.4 it is stated that a completely randomized design will be used, and there is no mention of the possibility of other designs. CVM requests that the protocol state that other appropriate designs may be used wherever the study design is discussed. For example, the third sentence of Section 3.2.1 can be reworded as (changes in italics), "Allocation of fish-to-tanks will be done following a completely randomized design *or other appropriate design.*"
2. Section 5.5.1 states that sample counting may be done by masked or unmasked personnel. This is acceptable for those doing pre-treatment sample counting. However, those counting fish at the end of post-treatment, regardless of what counting method they use, should be masked to treatment.
3. Section 6.1.4.1 states that on rare occasions a sample count may be done at the end of post-treatment. However, it does not indicate from which tank(s) the sample of fish will be selected to do the count. CVM recommends that, if this procedure is used, a sample be selected from each tank and its weight applied to only that tank when estimating the number of fish in the tank.
4. The last sentence in the "Actual counts at the end of the study" part of Section 6.1.4.2 states, "Results from hand-counting fish from experimental units will be added to the total mortality in each of the test tanks, resulting in an accurate number of fish/test tank at the start of the study." Please explain the purpose of this statement. It implies that when live fish are hand-counted at the end of the study, the estimated total fish count at the start of the study will be replaced with the sum of the mortality count and the live fish hand count.
5. Assumption 2 in Section 7.3.3 states that the equality of the variances between the two treatment groups is known. The analysis will be done on proportions, and the variance of the mean changes according to the proportion. Therefore, this assumption is not correct. Please remove this assumption from Section 7.3.3.
6. The protocol indicates several times that the tank will be treated as the experimental unit. However, the protocol does not indicate that this will be done in the analysis. We recommend that in Section 7.3.4 the protocol state that tank will be treated as the experimental unit in the analysis. Remember that tank can be treated as the experimental unit in the generalized linear model analysis, for example, in SAS Proc GLIMMIX. To do so, enter the response in the model statement as the ratio of the number of mortalities divided by the total number of fish in the tank.
7. In the generalized linear model analysis, the mean square error should be multiplied by the overdispersion parameter. This can be done, for example, in SAS Proc GLIMMIX by

including a "random residual" statement. Please indicate in Section 7.3.4 that in the analysis the mean square error will be multiplied by the overdispersion parameter.

#### ADDITIONAL COMMENTS

We offer the following recommendations for revision of your protocol and points for consideration. While not required for concurrence of this protocol, we believe that incorporating these recommendations will improve the quality of this study protocol and future protocols.

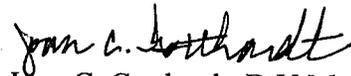
1. In Section 3.3, the protocol provides a table with the number of studies to be conducted. We agree that this reflects the minimum number of studies needed to supplement data from the United States Geological Survey Upper Midwest Environmental Sciences Center (UMESC) to complete the effectiveness technical sections for control of mortality in coolwater species of freshwater-reared finfish due to bacterial gill disease and in warmwater species of freshwater-reared finfish due to external columnaris. The table in the protocol indicates that you will conduct one pivotal and one supportive study in any coolwater species; you should use a different species in each study. For the warmwater species, CVM encouraged UMESC to select a species that is commonly raised in aquaculture facilities in the United States such as hybrid striped bass. Depending on doses used for certain species or lifestages, additional target animal safety data may be required.
2. Your protocol defines the causative agent of bacterial gill disease to genus (*Flavobacterium spp.*) If you wish for the indication to match that which is currently approved for freshwater-reared salmonids, "control of mortality... due to bacterial gill disease associated with *Flavobacterium branchiophilum*," then your studies will need to confirm the presence of this species of bacteria.
3. The proposed method of disease diagnosis is acceptable for this protocol, but definitive diagnosis (for instance, by bacterial culture) using at least a subset of samples is preferable.
4. Section 1.2 of the protocol says that the manufacturing sponsor would ultimately like the label indication for 35% PEROX-AID to be "Use as an external microbicide for all freshwater-reared finfish eggs and freshwater-reared finfish." We remind you that CVM approves claims for specific diseases and etiologic agents for which there is substantial evidence that the drug is effective in controlling or treating the disease or controlling mortality due to the disease. For a claim as an "external microbicide," a sponsor would need to demonstrate that the drug is effective against all microorganisms that can potentially cause disease in fish.
5. Fourteen days is an acceptable length for a post-treatment period without re-infection. In certain circumstances, a post-treatment period between 10 and 14 days may be acceptable. If you analyze data at 10 days post-treatment as described in Section 3.2.4, you will need to provide an adequate and acceptable justification for the decision to shorten the post-treatment in the final study report.

6. Section 4.4 states that all completely randomized design procedures will follow SOP MISC 327 in Appendix E. We believe that you intended to reference SOP MISC 237. Please correct this typographical error.
7. In Section 5.1.2.2, to avoid confusion, please indicate who will calculate the loading rate. Currently, the protocol says "we will mathematically calculate..." and is therefore ambiguous.
8. Section 5.7 indicates that subjects will be removed from experimental units using dip nets that are sanitized before and after use with disinfectant. Please provide more instruction on the disinfection step to ensure that disinfectant does not contaminate the water in the experimental units and contribute to target animal toxicity. For instance, an acceptable explanation would be that the nets will be rinsed with water before use.
9. In Section 5.9.3, the protocol states that if it is not possible to measure hardness, alkalinity, or pH, that it will be acceptable to report historical data. Water quality parameters should be measured during the study.
10. There is no place on Form 1 or other forms to record the water temperature and DO of the reference population tank. Since the protocol calls for this measurement, there should be a place on one of the forms for this information, unless it will be documented in facility records that will be copied for inclusion in the final study report.
11. It would also be appropriate to have a place on Form 1 to report the frequency and number of treatment administrations.
12. In your correspondence to us dated October 9, 2007, you indicated that the use of 35% PEROX-AID under INAD 011669 for the control of mortality caused by BGD and external columnaris would be limited to use at a single facility (Richloam State Hatchery, FL) on a limited number of species. The current protocol is not specific for Richloam State Hatchery and the species listed in your correspondence dated October 9, 2007. Should you wish to conduct studies at other facilities on additional species, please request a categorical exclusion for these facilities and be sure that the species fall under your authorization. We are in the process of evaluating your request for a slaughter authorization dated September 6, 2007, and amendment dated October 9, 2007.
13. Section 13 of the protocol says that unused drug remaining at the end of a study can be kept on-site for future use according to the Service's Study Protocol for Compassionate Aquaculture INAD Exemption under INAD 011669. We have not received a compassionate protocol for BGD and columnaris from you for this INAD. You indicated in your correspondence dated October 9, 2007, that use of the drug under this INAD for control of mortality due to BGD and columnaris would be pivotal in nature. Additionally, your previous correspondence indicates that bacterial and ectoparasite trials will be done at separate facilities. This section of the protocol should not say that the drug will be used in compassionate studies if there is to be no such use of this drug in that manner. Similarly, please remove reference to compassionate protocol use in Section 5.2.1.

We recommend that you submit a revised protocol for our review to obtain our concurrence before you begin this study. Our concurrence with your protocol would mean we fundamentally agree with the design, execution, and analyses proposed in your protocol, and that we commit that we will not later alter our perspectives on these issues unless public or animal health concerns appear that we did not recognize at the time of the protocol assessment. However, even with our concurrence, we could make no commitment that the data obtained from a study implementing your protocol will support an approval.

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 301-827-7571 or Dr. Donald Prater, Aquaculture Drugs Team Leader, 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



# United States Department of the Interior



U.S. FISH & WILDLIFE SERVICE  
AQUATIC ANIMAL DRUG APPROVAL PARTNERSHIP PROGRAM  
4050 BRIDGER CANYON ROAD  
BOZEMAN, MT 59715  
PHONE 406-994-9905/FAX 406-582-0242

September 26, 2007

Dr. Joan Gotthardt  
Director, Division of Therapeutic Drugs  
for Food Animals  
Document Control Unit, HFV-199  
Center for Veterinary Medicine  
7500 Standish Place, MPN-2  
Rockville, MD 20855

Dear Dr. Gotthardt:

The purpose of this submission is to request a formal review of the enclosed pivotal efficacy Study Protocol titled "The efficacy of 35% PEROX AID<sup>®</sup> to control mortality due to bacterial gill disease or external columnaris in cool and warmwater finfish." The Study Protocol is identified by Study Protocol Number H2O2-07-EFF. Please note that this protocol is nearly identical to Study Protocol CHLT-07-EFF, which received protocol concurrence from CVM on July 26, 2007 (I-009321-E-0086-OT). Use of 35% PEROX AID<sup>®</sup> in pivotal field efficacy trials will be conducted under the U. S. Fish and Wildlife Service's 35% PEROX AID<sup>®</sup> (hydrogen peroxide) compassionate INAD 11-669. Efficacy data generated from these studies will be used to support an expansion of the FDA-approved label claim for this aquaculture drug. We refer to your file number 11-669 dated September 11, 2007.

The current sponsor of INAD 11-669 is Dr. David Erdahl, Branch Chief, U. S. Fish and Wildlife Service, AADAP Program, 4050 Bridger Canyon Road, Bozeman, MT 59715. We would like to thank you in advance for your time and consideration with respect to the above described request. If you have questions, please contact Dr. Erdahl at (406)-994-9904.

Sincerely,

Dr. David Erdahl  
Branch Chief, AADAP Program

Enclosure: 3 copies of Study Protocol H2O2-07-EFF

