

Comment 2: Sections 6 and 9 of the protocol state that fish will be sample counted at the beginning of the exposure period and weekly during the exposure period to determine the mean weight of the study fish. This information will be recorded on Form 20. Neither Sections 6 or 9 nor Form 20 state the number or minimum number of fish that will be collected for sample counts. We recommend collecting at least 10 fish from each surrogate tank when each sample count is conducted. Please revise the protocol with regard to this comment.

AADAP Response – During weekly sample counts of the surrogate test tanks, all fish in each tank will be collected and weighed. The text in Section 9.10.4 Surrogate test tanks has been revised to state “the mean weight of all fish in each surrogate tank will be determined.” In addition, Form 20 has been revised to state the “total weight of all fish” and that “All fish will be collected from each surrogate tank for sample counting procedures.”

Comment 3: The final paragraph in Section 9.8.7.2 states that all fish in a tank will be collected for histology if less than 10 fish remain in a tank on Day 21. The correct day is Day 29. Please change 21 to 29.

AADAP Response – The incorrectly stated Day 21 in Section 9.8.7.2 End of in-life phase sampling has been changed to Day 29.

BIostatistics COMMENTS

Comment 1: Regarding the SAS code in Section 10.5, in the model statement, each tank will have a single response entered: the number of events (such as cumulative mortality) that occurred in the tank divided by the total number of events possible. Therefore, the random intercept statement specifying the option “subject=tank” is not necessary. Please remove this statement from the code.

AADAP Response – The following line “Random intercept / subject = tank group = trt” has been removed from the protocol.

Comment 2: Regarding the calculation of feed amounts discussed in Sections 6.4 and 9.10.4, the protocol does not explain how the weight/fish in the surrogate tanks and the fitted nonlinear equation relating age and weight will be used to determine the feed amounts. To provide this explanation, please make the following changes to Section 9.10.4:

At the end of the first paragraph of this section, please insert the following text: “To do this calculation, the fitted nonlinear equation discussed in Section 6.4 will be solved for X (age) in terms of Y (weight), and the estimated age of the fish will be calculated by substituting the mean weight/fish for Y in the inverted equation. The resulting estimate will be the assumed age of the fish on Day 1. The age of the fish on Days 2-7 will be determined by adding the numbers 1-6, respectively, to the estimated Day 1 age.”

After the first sentence in the second paragraph, please insert the following sentence: “This adjustment will be done by substituting the mean weight/fish for Y in the inversion of the fitted nonlinear equation and using a procedure analogous to the one done for Days 1-7.”

Therefore, the entire section should read:

“On the first day of the exposure period, the mean weight/fish in surrogate tanks ($n = 4$) will be determined, and this value will be used to calculate the amount of feed offered to fish in test tanks for the first week of the exposure period. To do this calculation, the fitted nonlinear equation discussed in Section 6.4 will be solved for X (age) in terms of Y (weight), and the estimated age of the fish will be calculated by substituting the mean weight/fish for Y in the inverted equation. The resulting estimate will be the assumed age of the fish on Day 1. The age of the fish on Days 2-7 will be determined by adding the number 1-6, respectively, to the estimated Day 1 age.

“The mean weight/fish in surrogate tanks will be determined weekly (Form 20), and feed amount offered to fish in test tanks will be adjusted accordingly (Form 8). This adjustment will be done by substituting the mean weight/fish for Y in the inversion of the fitted nonlinear equation and using a procedure analogous to the one done for Days 1-7. If necessary, feed amounts will be reduced in test tanks in which mortality is observed.”

AADAP Response – Section 9.10.4 Surrogate test tanks has been revised by inserting the text that was recommended by CVM reviews (i.e., the exact text from above was inserted in the appropriate places of the paragraphs).

Comment 3: The last sentence in Section 10.7 states, “Commonly used, commercially available statistical software packages, such as those used in this study, will not be validated.” This sentence may be intended to mean that you will not validate the software packages yourself, but it could be interpreted to mean that the software packages themselves are not validated. We understand that SYSTAT and SAS are validated software programs, and we do not require sponsors to validate them, nor do we validate them ourselves. Therefore, we request that the last sentence of Section 10.7 be omitted from the protocol.

AADAP Response – The last sentence in Section 10.7 Statistical software to be used has been removed.

ADDITIONAL COMMENTS

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

Comment 1: Sections 5 and 8 include the word “therapeutic” to describe the 17MT dose. The word “therapeutic” describes something that is for or related to the treatment of disease. 17MT is intended to manipulate the gender of tilapia, which is not a disease treatment. We recommend removing the word “therapeutic” from Sections 5 and 8 of the protocol.

AADAP Response – The word “therapeutic” has been replaced with “efficacious” in Section 5 STUDY OBJECTIVE(S) and Section 8 EXPERIMENTAL DESIGN.

Dr. Cindy Burnsteel - 4

The current sponsor of INAD 11-236 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. Thank you for taking the time to review the enclosed amended target animal safety protocol numbered 17MT-09-TAS.1. If you have any questions, please contact Dr. Erdahl at (406) 994-9904.

Sincerely,

 for Dave Erdahl

Dr. David Erdahl
AADAP Program – Branch Chief
dave_erdahl@fws.gov

Enclosures: 3 copies of Study Protocol Number 17MT-09-TAS.1, as revised August 03, 2009





Dave Erdahl/R6/FWS/DOI
07/29/2009 10:25 AM

To jim_bowker@fws.gov, molly_bowman@fws.gov,
dan_carty@fws.gov, niccole_lawson@fws.gov,
miranda_dotson@fws.gov
cc
bcc

Subject Fw: ERA Request (NFA Code 077): I-011236-E-0059-TS

FYI.....not sure if any of you received this or not?? If not, wasn't the AADAP/ERA process supposed to be set-up so not only DE received notification??

de

----- Forwarded by Dave Erdahl/R6/FWS/DOI on 07/29/2009 10:23 AM -----



"CVM_ONADE_NOTICE_HF
V-130"
<CVM_ONADE_NOTICE_HF
V-130@fda.hhs.gov>
07/29/2009 10:04 AM

To <dave_erdahl@fws.gov>
cc "CVM_ONADE_NOTICE_DCU"
<CVM_ONADE_NOTICE_DCU@fda.hhs.gov>
Subject ERA Request (NFA Code 077): I-011236-E-0059-TS

Re: ERA Request for I-011236-E-0059-TS

Dear Dr. Erdahl:

We request an end-review amendment (ERA) for your protocol dated June 10, 2009 (E-0059), because we have determined that additional information may allow us to concur with this protocol. The protocol is entitled "A Research Protocol to Determine: The Safety of 17 α -Methyltestosterone Administered in Feed to Tilapia (*Oreochromis* spp.)" (17MT-09-TAS.1). You submitted this protocol to the investigational new animal drug (INAD) file I-011236 for 17 α -methyltestosterone (17MT) medicated feed. The drug is proposed for gender manipulation in tilapia. The deadline for receiving your ERA to this submission is August 8, 2009 (ERA due date).

Submit the complete, revised protocol with all changes highlighted within the text of the protocol, including minor modifications necessary during the incorporation of the changes we requested (e.g., section numbering, pagination). Please also provide written certification either in the cover letter or in the 'other comments' section of an electronic submission, that, with the exception of the highlighted protocol changes, the text of the protocol found in the ERA is identical to the text of the protocol submitted on June 10, 2009, and that no other text changes beyond those highlighted have been made. If you do not highlight protocol changes and certify the protocol as directed, we will not review the ERA.

In the amendment, please address the following comments. Please do not submit information other than that requested. The submission of information that we do not request may lead to our refusal to review the ERA.

1. Section 9.10.1 of the protocol states that fish will be allocated from the reference tanks to the study tanks in rounds. AADAP SOP MISC 239 states that if more than one reference population tank is used, then the number of transfer rounds will be distributed as evenly as possible among the reference tanks. Because of the information in the SOP, the fish should be allocated in at least two rounds. Please revise the protocol to state the number of rounds or the minimum and maximum number of rounds used to allocate fish to the study tanks.
2. Sections 6 and 9 of the protocol state that fish will be sample counted at the beginning of the exposure period and weekly during the exposure period to determine the mean weight of the study fish. This information will be recorded on Form 20. Neither Sections 6 or 9 nor Form 20 state the number or minimum number of fish that will be collected for sample counts. We recommend collecting at least 10 fish from each surrogate tank when each sample count is conducted. Please revise the protocol with regard to this comment.
3. The final paragraph in Section 9.8.7.2 states that all fish in a tank will be collected for histology if less than 10 fish remain in a tank on Day 21. The correct day is Day 29. Please change 21 to 29.

Biostatistics Comments

1. Regarding the SAS code in Section 10.5, in the model statement, each tank will have a single response entered: the number of events (such as cumulative mortality) that occurred in the tank divided by the total number of events possible. Therefore, the random intercept statement specifying the option "subject=tank" is not necessary. Please remove this statement from the code.
2. Regarding the calculation of feed amounts discussed in Sections 6.4 and 9.10.4, the protocol does not explain how the weight/fish in the surrogate tanks and the fitted nonlinear equation relating age and weight will be used to determine the feed amounts. To provide this explanation, please make the following changes to Section 9.10.4:
At the end of the first paragraph of this section, please insert the following text: "To do this calculation, the fitted nonlinear equation discussed in Section 6.4 will be solved for X (age) in terms of Y (weight), and the estimated age of the fish will be calculated by substituting the mean weight/fish for Y in the inverted equation. The resulting estimate will be the assumed age of the fish on Day 1. The age of the fish on Days 2-7 will be determined by adding the numbers 1-6, respectively, to the estimated Day 1 age."
After the first sentence in the second paragraph, please insert the following sentence: "This adjustment will be done by substituting the mean weight/fish for Y in the inversion of the fitted nonlinear equation and using a procedure analogous to the one done for Days 1-7."
Therefore, the entire section should read:
"On the first day of the exposure period, the mean weight/fish in surrogate tanks ($n = 4$) will be determined, and this value will be used to calculate the amount of feed offered to fish in test tanks for the first week of the exposure period. To do this calculation, the fitted nonlinear equation discussed in Section 6.4 will be solved for X (age) in terms of Y (weight), and the estimated age of the fish will be calculated by substituting the mean weight/fish for Y in the inverted equation. The resulting estimate will be the assumed age of the fish on Day 1. The age of the fish on Days 2-7 will be determined by adding the number 1-6, respectively, to the estimated Day 1 age."
"The mean weight/fish in surrogate tanks will be determined weekly (Form 20), and feed amount offered to fish in test tanks will be adjusted accordingly (Form 8). This adjustment

will be done by substituting the mean weight/fish for Y in the inversion of the fitted nonlinear equation and using a procedure analogous to the one done for Days 1-7. If necessary, feed amounts will be reduced in test tanks in which mortality is observed.”

3. The last sentence in Section 10.7 states, “Commonly used, commercially available statistical software packages, such as those used in this study, will not be validated.” This sentence may be intended to mean that you will not validate the software packages yourself, but it could be interpreted to mean that the software packages themselves are not validated. We understand that SYSTAT and SAS are validated software programs, and we do not require sponsors to validate them, nor do we validate them ourselves. Therefore, we request that the last sentence of Section 10.7 be omitted from the protocol.

Additional Comment

We offer the following recommendation for revision of your protocol. While not required for concurrence of this protocol, we believe that incorporating this recommendation will improve the quality of this study protocol and future protocol submissions.

Sections 5 and 8 include the word “therapeutic” to describe the 17MT dose. The word “therapeutic” describes something that is for or related to the treatment of disease. 17MT is intended to manipulate the gender of tilapia, which is not a disease treatment. We recommend removing the word “therapeutic” from Sections 5 and 8 of the protocol.

If we receive your ERA by the ERA due date, we will determine if it is acceptable for review. If your ERA is acceptable for review, we will review it as part of your pending submission and will issue a letter concerning the acceptability of your protocol. If your ERA is not acceptable for review, we will not review it and will issue a refuse to review letter. In addition, we will issue a non-concurrence letter for your original protocol.

If we do not receive an ERA or receive it after the ERA due date, we will issue a non-concurrence letter for your original protocol. We will not review an ERA received after the ERA due date and will issue a refuse to review letter.

If you submit an ERA, please reference the principal submission identifier found in the reference line of this email. If you have any questions, please contact me at (240) 276-8341 or Dr. Jennifer Matysczak, Leader, Aquaculture Drugs Team, at (240) 276-8338.

Sincerely,

Cindy L. Burnsteel, DVM
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

June 10, 2009

Dr. Cindy L. Burnsteel, 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

Subject: 17- α Methyltestosterone (MT) INAD 11-236; Target Animal Safety Research Protocol

Dear Dr. Burnsteel:

The purpose of this submission is to request a formal review of the enclosed target animal safety (TAS) study protocol titled "The Safety of 17 α -Methyltestosterone Administered in Feed to Tilapia (*Oreochromis* spp.)." The study protocol is identified by Study Protocol Number 17MT-09-TAS.1. We refer to file number I-011236-E-0022-OT, dated February 06, 2007.

The current sponsor of INAD 11-236 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. Thank you for reviewing the enclosed 17- α Methyltestosterone TAS study protocol. Please contact Dr. Erdahl (406-994-9904) if you have questions or need additional information.

Sincerely,

Dr. David Erdahl
Branch Chief, AADAP Program

Enclosure: 3 copies of Study Protocol Number 17MT-09-TAS.1

