DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

I-011741-P-0053-TS

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

Re: Target Animal Safety Study AQS20E-11-TAS-FISH-02

Dear Dr. Erdahl:

Based upon the information you submitted on June 11, 2013, and amended on October 29, 2013 (T-0058), we consider the Target Animal Safety technical section to be complete. The technical section is complete for the use of AQUI-S 20E (eugenol) solution administered at a dose of 40 mg eugenol/L for the sedation of freshwater salmonid finfish to a handleable condition. The Target Animal Safety technical section for freshwater nonsalmonid finfish remains incomplete.

TARGET ANIMAL SAFETY

This technical section complete letter represents our finding that study AQSE-11-TAS-FISH-02 essential to determining target animal safety is complete and accepted. We also evaluate target animal safety in our review of other technical sections, particularly the Effectiveness and All Other Information technical sections.

We have the following comments.

GENERAL COMMENTS

1. In buckets in which fish were exposed to 0 mg/L and were not sedated when moved from exposure to recovery containers, you collected all the fish by pouring them through a net and collecting the water to determine dissolved oxygen (DO) and water temperature. The agitation of the water during the pouring could have altered the DO. In future studies, please collect DO measurements before agitating the water. The FOI Summary reflects DO results from the beginning of the exposure only and not a mean of beginning and end.

2. Tank 11 (0X T2) contained a small amount of eugenol where it should have contained none. You did not provide an adequate explanation of how this could have happened. We did not feel it affected the results of the study; however, in the future, please explain events such as these in more detail.

3. You did not provide an interpretation of the histopathology findings. In the future, please do not just list the findings of the histopathologist, but instead provide a broader interpretation of the overall results of the study.

BIOSTATISTICS COMMENT

Following the protocol, you generated 95% confidence intervals (CIs) for each exposure regimen using the arcsine square root transformation. We note that the intervals are wide because the CIs were calculated separately, and there are only 3 observations per exposure regimen. An alternative to separate calculations is to generate model-based estimates using a generalized linear model. The model would have dose as a fixed effect, and duration and the dose × duration interaction as covariates. The model would also assume a binomial distribution and employ a logit link. We performed this analysis and also generated (back-transformed) least squares means and 95% CIs for each exposure regimen. This method gains efficiency by using all data in one analysis instead of individually analyzing the results from each regimen. The results are presented in Table 2 of the Freedom of Information summary.

ADDITIONAL COMMENT

Thank you for providing all the information in the requested amendment. We have reviewed the dosing errors for the effectiveness studies and have determined that it does not affect our conclusions regarding the Effectiveness technical section.

DRAFT LABELING

Please submit draft labeling sections pertaining to the Target Animal Safety technical section when you submit your Target Animal Safety technical section request for the sedation to handleable claim in freshwater nonsalmonid finfish.

FREEDOM OF INFORMATION (FOI) SUMMARY

We appreciate your cooperation by including the relevant portions of the FOI Summary with this submission. A copy of the draft Target Animal Safety section of the FOI Summary is enclosed. Please review the FOI Summary for accuracy and notify us if you find any errors.

ALL OTHER INFORMATION (AOI)

Please include “all other information” pertaining to target animal safety of eugenol in freshwater finfish when you request a Target Animal Safety technical section complete for freshwater finfish. If there is no information available, please note in your cover letter that you are not aware of any additional information pertaining to the safety of eugenol in freshwater finfish.

If you submit correspondence relating to this letter, you should reference the date and the principal submission identifier. If you have any questions or comments, please contact me at 240-402-0817. You may also contact Dr. Jennifer Matysczak, Leader, Aquaculture Drugs Team, at 240-402-0588.

Sincerely,

{see appended electronic signature page}
Cindy L. Burnsteel, DVM
Director, Division of Therapeutic
Drugs for Food Animals
Office of New Animal Drug Evaluation
Center for Veterinary Medicine

Enclosure:
Draft Target Animal Safety section of the FOI Summary

Electronic Signature Addendum for Submission ID

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Signing Authority (Role)	Letter Date
Cindy Burnsteel (Division Director)	12/10/2013

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