DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

I-011741-P-0059-TS
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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 Studies AQS20E-11-TAS-FISH-04, AQS20E-11-TAS-FISH-03

Dear Dr. Erdahl:

Based upon the information you submitted on December 3, 2013 (P-0059; AQS20E-11-TAS-FISH-04; channel catfish), and December 12, 2013 (P-0060; AQS20E-11-TAS-FISH-03; yellow perch), 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 100 mg eugenol/L for the sedation of freshwater nonsalmonid finfish to a handleable condition.

TARGET ANIMAL SAFETY

This technical section complete letter represents our finding that studies AQSE-11-TAS-FISH-03 and AQS20E-11-TAS-FISH-04 essential to determining target animal safety are 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 both studies, in buckets in which fish were exposed to 0 mg/L and fish 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 draft FOI Summary section reflects DO results from the beginning of the exposure only and not a mean of beginning and end.

2. We note that during the making of the bulk solution in study AQS20E-11-TAS-FISH-04, the 150 mg/L tub in replicate 3 had an analytically verified eugenol concentration that was 6.4% above target. Based on this, you elected to dilute the solution to bring it within 5% from target. The protocol allowed for a 25% difference from target and was set *a priori*. Adjusting the bulk concentration down may have

introduced bias towards less mortality. If you felt a tighter concentration was necessary, this should have been laid out in the protocol. The small difference in concentration did not likely affect the results and the initial concentration was still within the confines of the protocol; however, *a priori* parameters should not be adjusted in future studies.

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 and Table 5 of the draft FOI Summary section. This reanalysis affected our conclusions in study AQS20E-11-TAS-FISH-04 and we determined that the maximum safe exposure time for channel catfish would be 2.5 minutes for 150 mg eugenol/L.

DRAFT LABELING

In the future, please include draft labeling when you submit a Target Animal Safety technical section.

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)

The “all other information” provided in this submission is acceptable. You do not need to resubmit the information submitted again.

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