DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Food and Drug Administration
Rockville MD 20857

I-011741-P-0050-EF

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: Effectiveness technical section complete

Dear Dr. Erdahl:

Based upon the information you submitted on November 20, 2012, we consider the Effectiveness technical section to be complete. The technical section is complete for the use of eugenol for the sedation of freshwater finfish to a handleable condition. The low end of the dose range, as supported by effectiveness data, will be 25 mg eugenol/L for salmonid finfish and 40 mg eugenol/L for nonsalmonid finfish.

LABELING

We reviewed the sections of your draft labeling related to effectiveness. We did not review any labeling text associated with target animal safety, human food safety, environmental safety, user safety, or chemistry, manufacturing, and controls. We have suggested labeling changes below. However, if you have comments or concerns about our changes, we encourage you to discuss them with us. CVM may request additional revisions after reviewing the other technical sections.

Middle Panel: Front

1. Please change the indication to: "For sedation of freshwater finfish to a handleable condition."

Middle Panel: Back, Right Panel

Since we have a number of comments and suggested changes for these panels, we have summarized the issues below and then provide suggested text for these two panels.

1. Please remove the "For all freshwater finfish" at the top of all panels, as this is already included in the Indication.

2. Please change the Indication to "For sedation of freshwater finfish to a handleable condition."

3. In the Directions for Use text, you provided AQUI-S 20E and eugenol doses, but in the table, you provided only AQUI-S 20E doses. Doses on the label should be presented only as the active ingredient, not as the dose of the product. However, the final volume to be administered, as presented below, should be based on volume of the product.

4. In the Directions for Use text, you suggested the following indication language "…until the desired level of sedation has been achieved." During effectiveness studies only one level of sedation was measured, sedation to a handleable condition, thus you should only use that terminology on the label.

5. Please remove the statement about AQUI-S 20E being 100% active ingredient. This is incorrect, and information about the concentration should be presented with the calculations.

6. In your submission, you did not provide information on how the approximate mean times to handleable or the median times to recover were calculated for the table. It may be unclear whether a user would understand how the values were obtained, and whether the values were actually limits (i.e., at 25 mg/L a fish can only be kept in the sedative for 2.0 minutes). Additionally, labels should not list two effective point doses (for non-salmonids) and a range without further information on how a user should pick a dose. We recommend that you delete the table and replace it with text that describes what to expect with sedation and recovery times. We have suggested language in the complete text of the panels below.

7. In your submission, you did not indicate whether this product would have additional labeling, such as a package insert or an outsert accompanying the immediate container label. We recommend that the labeling include a package insert or an outsert where information from field effectiveness and target animal safety trials can be presented. This would allow the end user to formulate their own thoughts on what dose to pick based on water conditions and species. A table could include information on fish species tested, water temperature, all doses tested during field trials, and the mean range of times for sedation to a handleable condition and mean range of times to recovery. If you agree with a package insert or outsert, please include the language for it with future technical section requests. We would be happy to work with you on developing this labeling.

8. The proposed calculation formula has units in grams on the right side, but the units do not cancel each other out on the left side to give grams, making the equation mathematically untrue. While we understand the value of having one formula for ease of use, it does not inform the user how to properly calculate the amount of drug needed. You also presented specific gravity information on the Right Panel. This was not used in the calculations during your effectiveness studies; please remove it from the label. Please place all information needed for calculation on one panel.

9. Because AQUI-S 20E is proposed as an over-the-counter product, more detailed instructions are needed to inform the end user how to use a sedative. The label should include instructions on how to sedate and recover fish, describe how to determine when a fish is sedated to a handleable condition and recovered, and describe general sedation practices (i.e., standards of care).

10. During the effectiveness studies, no adverse events related to fish being exposed to sunlight or wind were noted. Please provide additional information to support your proposed statement regarding this issue in the Target Animal Safety technical section.

11. You suggested text about maintaining dissolved oxygen, temperature, and pH within 80% of acclimated levels. We believe that a 20% change in these values may not be safe for the fish. Below, we have revised this language and moved it to the section describing procedures for sedating and recovering fish.

12. Headshaking, along with other abnormal behaviors, was seen in all species of fish, not just salmonids. Please correct this statement on the label.

13. The effectiveness field studies did not evaluate whether eugenol provides any analgesia. A statement regarding this should be added. Additionally, the studies did not employ invasive procedures or test surgical anesthesia levels. A statement should be added that states invasive procedures should not be performed on fish sedated only to a handleable condition. We have provided suggested text for both of these issues below.

Recommended text for the label (for the "Middle Panel: Back" and "Right Panel" sections):

INDICATION: For sedation of freshwater finfish to a handleable condition
Not for use in brackish or saltwater.
Freshwater finfish includes any finfish living in freshwater at the time of treatment.

DIRECTIONS FOR USE: Expose freshwater salmonid finfish at 25 to 40 milligrams (mg) eugenol per liter (L) in a static bath until the fish become handleable. Expose non-salmonid freshwater finfish at 40 to 100 mg eugenol per L in a static bath until the fish become handleable.

Under tested conditions, freshwater finfish were sedated within 5 minutes (mean approximately 1 – 3 minutes) when exposed to the low end of the dose range. Under tested conditions, freshwater finfish recovered on average in 4 to 12 minutes when exposed to the low end of the dose range.

CALCULATIONS:
The amount of AQUI-S 20E required for sedation is dependent on the volume of water treated. Once the volume of water to be treated and the intended eugenol dose has been determined, use the following steps to determine the correct quantity of AQUI-S 20E required for treatment.

If volume of water to be treated is known in gallons, calculate the equivalent number of liters (L):

Number of gallons x 3.79 liters/gallon = X liters
Example: 20 gallons x 3.79 liters/gallon = 75.8 L

With a known volume, in liters, and a known intended dose, calculate the number of milligrams (mg) of AQUI-S 20E needed:

Target eugenol dose (mg/L) x Treatment volume (L) = X mg of eugenol
Example: 25 mg/L eugenol x 75.8 L = 1,895 mg eugenol

AQUI-S 20E is 10% active, meaning it contains 100 mg eugenol/ milliliter. Calculate the number of milliliters (ml) of AQUI-S 20E needed.

(X mg eugenol) / (100 mg/ml) = X ml of AQUI-S 20E
Example: 1,895 mg eugenol / (100 mg/ml) = 18.95 ml of AQUI-S 20E;

19 ml of AQUI-S 20E is needed to sedate finfish at 25 mg/L eugenol in 20 gallons of water.

Table x. Amount (ml) of AQUI-S 20E to add to treatment water to achieve a target concentration of eugenol. mg/L = parts per million (ppm)

Target eugenol dose (mg/L or ppm)	**Volume of Treatment Water (gal)**							
	1	**5**	**10**	**15**	**20**	**25**	**50**	**100**
25	0.9 ml	4.7 ml	9.5 ml	14.2 ml	19.0 ml	23.7 ml	47.4 ml	94.8 ml
40	1.5 ml	7.6 ml	15.2 ml	22.7 ml	30.3 ml	37.9 ml	75.8 ml	151.6 ml
60	2.3 ml	11.4 ml	22.7 ml	34.1 ml	45.5 ml	56.9 ml	113.7 ml	227.4 ml
100	3.8 ml	19.0 ml	37.9 ml	56.9 ml	75.8 ml	94.8 ml	189.5 ml	379.0 ml

DIRECTIONS:

Procedures for sedating finfish to a handleable condition:

- Calculate dose using the formulas or Table 1 above.
- Always start with the minimum effective dose. Increase the amount of drug in measured increments, up to the maximum approved dose, until the fish is sedated to a handleable condition.
- Have all necessary equipment ready before beginning sedation procedure, including a separate recovery container with fresh water.
- Add AQUI-S 20E directly to the pre-measured volume of water in the container (e.g., bucket, tub) where finfish will be sedated. Stir to completely mix.
- If the fish is not already in the exposure container, gently move the finfish into the container containing AQUI-S 20E.
- Administer in a static bath, in an environment that is quiet and nonstimulatory.
- The water used for exposure should be the same or similar to water in which the fish are taken. The water should be well-oxygenated, and its temperature and pH should be similar to that of the water from which the fish are taken. Dissolved oxygen and temperature should be maintained throughout sedative exposure.
- Monitor fish behavior, gill ventilation, reaction time, and depth of sedation throughout sedation. Characteristics of finfish that have become too deeply sedated include decreased or absent gilling and no reaction to firm pressure on the body. If these signs are observed, remove the fish immediately and place in clean, flowing, well-oxygenated water.
- A finfish is sedated to a handleable condition when it can be easily handled and measured for length and weight with minimal to no movement. Finfish should only be exposed to AQUI-S 20E until they can be handled. Safety and effectiveness have not been demonstrated for longer exposures.

Procedures for recovering finfish:

- As soon as the handling procedure is complete, place finfish in a container with clean, flowing, well-oxygenated water.
- Throughout recovery maintain water parameters, including dissolved oxygen, pH, and temperature, at levels at which the finfish are housed prior to the sedation.
- Continue to monitor finfish behavior, gill ventilation, and reaction time throughout recovery.
- A finfish is considered recovered when it maintains an upright position, resumes normal swimming behavior, and can avoid obstacles in its pathway.
- Do not release finfish into waterways before they are fully recovered.

Animal Safety Warnings:

- Head-shaking, agitation, piping, and/or coughing may occur in finfish during sedation. It should only last a brief time after exposure to the drug.
- If gill ventilation stops before the procedure is over, remove the fish immediately from the AQUI-S 20E solution and place in clean, circulating water.

Additional Recommendations

- Do not leave fish unattended during sedation, or recovery, until completely recovered.
- Minimize stress (e.g. sudden environmental changes) prior to treatment.
- Avoid, if possible, feeding finfish before sedation.
- Do not sedate more fish than can be handled within a reasonable amount of time. Groups with a maximum of 10 finfish were tested in effectiveness field trials.
- Species, size and/or age of finfish, health status, and environmental factors such as water temperature may impact the time to sedation to a handleable condition and time to recovery. An initial bioassay on a small number of fish is recommended before sedating the entire group.
- Studies have not evaluated whether AQUI-S 20E provides analgesia (i.e., relief from pain) during exposure to the drug, or in periods following exposure.
- Invasive procedures (e.g., surgery) should not be performed on fish sedated to a handleable condition as these fish will not have achieved a level of anesthesia appropriate for surgery.

FREEDOM OF INFORMATION (FOI) SUMMARY

We prepared the Effectiveness section of the FOI Summary, and a copy is enclosed. Please review the FOI Summary for accuracy and notify us if you find errors.

ALL OTHER INFORMATION

The "all other information" provided in this submission is acceptable. You do not need to re-submit the information provided in this submission again. In the future, we recommend that you provide the search terms and list the databases searched when you submit AOI.

In your AOI, you referenced a paper on Pacific lamprey. The authors of the paper conclude that unless it can be demonstrated that the extreme agitation observed is not physiologically detrimental to the fish, they do not support the use of AQUI-S 20E for anesthesia of juvenile Pacific lampreys. Additionally, the lowest dose that the authors deemed effective was 100 mg eugenol/L; however, it took longer than 5 minutes to sedate the lamprey which was the endpoint for effectiveness in the field studies. Although 100 mg eugenol/L would fit within your proposed dose range for non-salmonid finfish, please discuss how we should address this safety information in labeling when you submit your Target Animal Safety technical section.

Include a copy of this technical section complete letter when you submit your new animal drug application. Please contact us if there are changes in the product development plan (e.g., indication, dosage, duration of use) or you become aware of any issues that may impact the status of this technical section or your application. We will make a final decision on whether we can approve your application after we have reviewed all of the data for all applicable technical sections and any other information available to us, as a whole, and determined whether the requirements for approval described in the Federal Food, Drug, and Cosmetic Act have been met.

If you submit correspondence relating to this letter, your correspondence should reference the date and the principal submission identifier. If you have any questions or comments, please contact me at 240-276-8341. You may also contact Dr. Jennifer Matysczak, Leader, Aquaculture Drugs Team, at 240-276-8338.

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 Effectiveness Section of the FOI Summary