DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

I-010541-G-0115 I-010541-G-0116 I-010541-G-0118

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

NOV 2 8 2006

Re: Status of effectiveness technical section for AQUI-S and review of draft label language

Dear Dr. Erdahl:

We have reviewed your submissions dated September 26, September 27 and September 28, 2005, to your investigational new animal drug (INAD) file for the use of isoeugenol (AQUI-S) to sedate freshwater-reared finfish.

You have completed the number of studies requested to demonstrate the effectiveness of 50% isoeugenol (AQUI-S) to sedate freshwater-reared finfish to handleable.

To obtain an effectiveness technical section complete, validation of the dose verification method used in pivotal effectiveness studies is required as discussed in a pre-submission conference between CVM and AQUI-S New Zealand, Ltd. (AQNZ) on February 7, 2006. Mr. Bowker attended this meeting. Additionally, we request draft FOI Summaries for the final study reports submitted to INAD 010541 files P-0031, P-0034, P-0035, P-0036, and P-0037. Please see the enclosed tables to correlate our submission identifiers with your study numbers. These tables are corrected and updated versions of the effectiveness study tables which you submitted for review. Finally, we reiterate our request in correspondence dated July 7, 2006 (I-010541-P-0114), that if you are aware of work done by others that is relevant to your effectiveness claim, whether the work may be supportive or contradictory, that you should submit this information to CVM while the effectiveness technical section is still open.

LABEL COMMENTS

Left Panel

1. "For animal treatments only" should be changed to "For freshwater-reared finfish treatment only" until claims are expanded to include shellfish or saltwater fish.

Middle Panel

2. On this panel and all other panels, please replace the word "fish" with "finfish" where the indications for product use are stated. CVM considers the term "fish" to include shellfish in addition to finfish.

3. The indication, as it appears on the middle and right panels, includes the word "anesthesia." Until anesthesia has been demonstrated, you should limit the phrase to "sedation to handleable" only.

4. The draft label language you submitted says the isoeugenol content of AQUI-S is 54% (w/w). However, in final study reports previously submitted, the isoeugenol concentration was reported to be 50%. Additionally, your SOP 230.1 (provided in I-010541-P-0114 and other final study reports) says that the active ingredient in AQUI-S is 50% isoeugenol. Pivotal studies should be conducted with the final marked formulation; otherwise, bridging studies may be necessary. Please identify the final market formulation and the formulation tested in the effectiveness trials in a future submission. The product label should reflect the final market formulation.

Right Panel

5. Under "Indications," the draft label reads, "To sedate representative coolwater freshwater fish…" Please remove the word "representative," and rephrase to "To sedate coolwater species of freshwater-reared finfish…" The same actions should be taken on the warmwater label.

6. In the draft label language for a coolwater freshwater-reared finfish claim, the first sentence of the Directions for Use section needs a correction. If the isoeugenol content is 50%, then the milligrams of isoeugenol per liter should be 10 to 30, not 20 to 30, to correlate with the 20 to 60 mg/L AQUI-S dose range proposed.

7. The high end of the dose range may be limited by target animal safety information. In this draft label language, you have proposed 60 mg/L as the highest dose. If target animal safety data reveals that 60 mg/L is unsafe, the upper limit of the dose range would need to be reduced, and 60 mg/L would need to be removed from the table(s) listing approximate times to handleable and recovery.

8. Please provide a spreadsheet that contains the data used to calculate the median times to handleable to assist us in assessing whether these times are valid. An alternative way to present the data would be to replace the median times and ranges with 80th percentile times; this approach has been used to illustrate time to handleable and time to recover in FOI summaries drafted for effectiveness studies. Other ways to illustrate the approximate times to effect and recovery can be considered as well. Regardless of the final presentation of expected times to handleable, please provide us with a spreadsheet that illustrates how you derived the numbers you intend to put on the label.

9. In correspondence dated April 28, 2006 (I-010541-P-0109), CVM noted that while in previous studies AQUI-S was measured for use in grams (as directed by the protocol), in

P-0109 AQUI-S was measured for use in milliliters. The directions for use on the label should include a conversion between grams AQUI-S and milliliters AQUI-S based on the amount of active ingredient in each of the two units. Since AQUI-S is a liquid solution that will be available over-the-counter if approved, it is likely that AQUI-S will be measured out in milliliters by a significant proportion of consumers. We note that the dose AQNZ provides as the product is marketed in other countries is in milliliters. Putting a conversion factor (or conversion calculation) on the label will help users more readily determine the correct dose required for their specific treatment.

10. After "Dilute AQUI-S at least 10-fold with water and shake vigorously to disperse AQUI-S and form a stock solution," the label should also say, "This solution must be used the same day that it is prepared." This would be in accordance with Directions of Use found on the AQNZ website and your SOP 230.1 indicates that solutions lose potency in a day.

Limitations and Cautions

11. As indicated in our correspondence to you dated November 21, 2005 (I-010541-P-0105), we ask that you rename the "Limitations and Cautions" section to "Precautions."

12. Your draft label language reads, "To facilitate recovery, place sedated fish in clean well-aerated water." Please change this to "To facilitate recovery, place sedated fish in clean, well-oxygenated water" to match your use of the phrase "well oxygenated water" elsewhere on the label. Please also note on the label that a recovery vessel should always be available; not having recovery water available once sedation or anesthetization is initiated could jeopardize the animal's life if overdose occurs.

13. Consider replacing the statement "Take into consideration life-stage and temperature of AQUI-S solution when sedating fish to handleable" with "Test in a small number before treating the entire group. Animal reaction to the anesthetic should be monitored carefully, noting gill ventilation, reaction time and depth of anesthesia. Start with a low concentration and increase the dose slowly depending on the handling procedure being carried out. Response to the anesthetic will depend on the species, the age and condition of the animals and environmental factors such as water temperature." (This has been adapted from the Directions for Use found on the AQNZ webpage.) If this substitution is not made, please explain further or reword the "take into consideration" phrase to provide the user with more specific information.

Additions

14. We remind you of CVM correspondence dated November 21, 2005 (I-010541-P-0105), which said that the label should reflect that safety testing has not been conducted in male and female broodfish; this can be done in the Precautions section.

15. In the same correspondence, CVM recommended that the following precaution be added to the label: "Vigorous head-shaking may occur in salmonids that is intermittent and usually lasts less than 30 seconds after exposure to AQUI-S." Even if target animal safety studies demonstrate safety in salmonids that exhibited headshaking, this precaution

should appear on the label to alert users to this behavior so that they are not alarmed if their fish headshake during treatment.

16. Your SOP 230.1 includes the following instructions: "Administer AQUI-S in a static bath." "Do not induce anesthesia in more fish than can be handled within a reasonable amount of time." Please include these directives on the label and rephrase "reasonable amount of time" if possible to provide clear instruction for users that are unfamiliar with the drug.

17. In a meeting held on November 13, 2001 (I-010541-Z-0009), AQNZ and U.S. Fish and Wildlife Service proposed, and CVM agreed, that the label should include a statement regarding supplemental oxygen for prolonged exposures (after 15 minutes). In the study I-010541-P0040, it was necessary to start supplemental oxygen after 9 minutes of exposure. Please add a recommendation for supplemental oxygen after a certain time period or when dissolved oxygen concentration is at or below a certain level to the label.

When you submit (target animal safety) final study reports in the future, please submit revised draft label language. Ideally, comments regarding your draft label language will be considered by AQNZ for incorporation into the final label submitted to CVM.

The draft label user safety information was not reviewed at this time.

If you submit correspondence relating to this letter, you should reference this letter by date and the principal submission identifier(s) found at the top of this letter. If you have any questions about this letter, please contact me at 301-827-7571, or Dr. Donald Prater, Leader, Aquaculture Drugs Team at 301-827-7567.

Sincerely,

Joan C. Gotthardt

Joan C. Gotthardt, D.V.M.
Director, Division of Therapeutic
Drugs for Food Animals
Office of New Animal Drug Evaluation
Center for Veterinary Medicine

Enclosures:
Efficacy Studies Tables 1-3

Table 1. Submitted pivotal and supportive field efficacy studies to support a claim for the use of AQUI-S on all freshwater-reared salmonids as submitted by AADAP in I-010541-G-0115 and updated by CVM, July 2006. "Pivotal" means that at least some, if not all of the data, in that study was accepted as pivotal.

STARS Number	FWS Study Number	Species	Life Stage	Temperature	Date Submitted by FWS	CVM Status
P-0031	AQUIS-01-EFF-01	Steelhead trout	Adult	6 °C	3/31/03	1/29/04 Supportive
P-0052 P-0088-FOI	AQUIS-01-EFF-02	Rainbow trout	Subadult Adult	8 and 15 °C	1/20/04 11/10/04	11/12/04 Pivotal
P-0042 P-0087 FOI	AQUIS-01-EFF.2-06	Chinook salmon	Fry Subadult	5 and 13 °C	10/2/03 11/9/ 04	7/30/04 Supportive
P-0103 (FOI Included)	AQUIS-01-EFF.2-14	Chinook salmon	Fry Juvenile	13 °C	5/10/05	2/17/06 Pivotal
P-0113 (FOI Included)	AQUIS-01-EFF.2-15	Kokanee salmon	Fingerling	10.3 and 15.4 °C	9/22/05	7/7/06 Pivotal
P-0105 (FOI Included)	AQUIS-01-EFF.2-16	Chinook salmon	Fingerling	10 and 15 °C	5/27/05	11/21/05 Pivotal
P-0114 (FOI Included)	AQUIS-01-EFF.2-19	Kokanee salmon	Juvenile	11 and 16 °C	9/23/05	7/7/06 Pivotal
P-0034	AQUIS-01-SUPP-EFF-01	Rainbow trout Lake trout Mountain Whitehead	subadult	9 °C	5/8/03	1/29/04 Supportive
P-0035	AQUIS-01-SUPP-EFF-02	Yellowstone Cutthroat trout	Adult	6 - 9 °C	5/9/03	1/29/04 Supportive
P-0036	AQUIS-01-SUPP-EFF-03	Bull trout	Subadult	9 °C	5/14/03	1/29/04 Supportive
P-0104 (FOI Included)	AQUIS-01-SUPP-EFF-06	Chinook salmon	Fry Juvenile	7 °C	5/26/05	10/13/05 Supportive
P-0099 (FOI Included)	AQUIS-01-SUPP-EFF-07	Rainbow trout GROUP	Fingerling	12 °C	4/20/05	1/20/06 Supportive

Table 2. Submitted pivotal and supportive field efficacy studies to support a claim for the use of AQUI-S on all warmwater freshwater-reared fish as submitted by AADAP in I-010541-G-0116 and updated by CVM, July 2006. "Pivotal" means that at least some, if not all of the data, in that study was accepted as pivotal.

STARS Number	FWS Study Number	Species	Life Stage	Temperature	Date Submitted by FWS	CVM Status
P-0061 P-0086-FOI	AQUIS-01-EFF.2-04	Channel catfish	Fry	6 and 12 °C	2/27/04 11/08/04	1/7/05 Supportive
P-0045 P-0082-FOI	AQUIS-01-EFF.2-07	Hybrid striped bass	Fry, fingerling, subadult	15 and 28 °C	11/14/03 10/25/04	9/23/04 Pivotal
P-0070 (FOI included)	AQUIS-01-EFF.2-08	Tilapia	Juvenile adult	23 and 32 °C	8/24/04	6/17/05 Pivotal
P-0071 (FOI included)	AQUIS-01-EFF.2-09	Channel catfish	Juvenile adult	20 and 30 °C	8/23/04	6/ 17/05 Pivotal
P-0037	AQUIS-01-SUPP-EFF-04	Hybrid striped bass	Subadult	27 °C	5/28/03	1/29/04 Supportive
P-0046 (FOI Included)	AQUIS-01-SUPP-EFF-05	Hybrid striped bass Tilapia Hybrid carp/goldfish	adult	26 °C	11/18/03 12/15/03	8/13/04 Supportive
P-0100 (FOI Included)	AQUIS-01-SUPP-EFF-08	Channel Catfish GROUP	juvenile	25 °C	4/21/05	1/30/06 Supportive

Table 3. Submitted pivotal and supportive field efficacy studies to support a claim for the use of AQUI-S on all coolwater freshwater-reared fish as submitted by AADAP in I-010541-G-0118 and updated by CVM, July 2006. "Pivotal" means that at least some, if not all of the data, in that study was accepted as pivotal.

STARS Number	FWS Study Number	Species	Life Stage	Temperature	Date Submitted by FWS	CVM Status
P-0040 P-0085-FOI	AQUIS-01-EFF-03	Shovelnose sturgeon	Subadult	12.5 and 21 °C	9/4/03 11/7/04	6/24/04 Pivotal
P-0078 (FOI Included)	AQUIS-01-EFF.2-03	Pallid sturgeon	Juvenile Subadult	12 and 18 °C	10/5/04	7/1/05 Pivotal
P-0047 P-0081-FOI	AQUIS-01-EFF-05	Largemouth bass	Fingerling subadult	6 and 12 °C	10/ 21/03 12/12/ 03 1/23/04 10/22/04	10/12/04 Supportive
P-0083 (FOI Included)	AQUIS-01-EFF.2-11	Smallmouth bass	Juvenile adult	12 and 18 °C	10/26/04	7/1/05 Pivotal
P-0092 (FOI Included)	AQUIS-01-EFF.2-12	Walleye	Juvenile	12 and 19 °C	1/27/05	11/10/05 Pivotal
P-0084 (FOI Included)	AQUIS-01-EFF.2-13	Largemouth bass	Juvenile adult	12 and 18 °C	11/9/04	7/1/05 Pivotal
P-0110 (FOI Included)	AQUIS-01-EFF.2-17	Walleye	Fingerling	18 and 22 °C	7/28/05	5/10/06 Pivotal
P-0117 (FOI Included)	AQUIS-01-EFF.2-18	June suckers	Fingerling	13 and 18 °C	9/27/05	7/7/06 Pivotal
P-0109 (FOI Included)	AQUIS-01-SUPP-EFF-09	Walleye	Broodstock	14 °C	7/19/05	4/28/06 Supportive
P-0111 (FOI Included)	AQUIS-01-SUPP-EFF-11	Walleye	Fingerling GROUP	22 °C	8/24/05	6/12/06 Supportive

United States Department of the Interior
FISH AND WILDLIFE SERVICE

AQUATIC ANIMAL DRUG APPROVAL PARTNERSHIP PROGRAM
4050 BRIDGER CANYON ROAD
BOZEMAN, MT 59715
(406) 587-9265/FAX 582-0242

September 26, 2005

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 list (Table 1) of pivotal and supportive AQUI-S® field efficacy studies that have been completed and submitted to CVM to support a label claim for the use of AQUI-S® on all freshwater salmonids. The table contains the following information:

1. Fish species and life-stages tested with AQUI-S®
2. Water temperatures at which studies were conducted
3. Dates individual Final Study Reports and Freedom of Information Summaries were submitted to CVM
4. Status of individual studies (if a CVM response has been received by AADAP)
5. CVM's tracking number (if a CVM response has been received by AADAP)

Based on numerous discussions and correspondence with CVM, we believe this data is sufficient to support the enclosed draft label (see attached Draft Label Claim for use of AQUI-S® on all Freshwater Salmonids). We refer to your file number INAD 10-541 P-0084 dated July 01, 2005.

The current sponsor of INAD #10-541 is Dr. David Erdahl, U.S. Fish and Wildlife Service, Acting Branch Chief - 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
Acting Branch Chief - AADAP Program

enclosures:

Table 1a. Submitted pivotal and supportive field efficacy studies to support a label claim for the use of AQUI-S® on all freshwater salmonids.

Study Number	Species and Life-stage Tested		Temperature	Date Submitted	Status	Tracking Number
AQUIS-01-EFF-01	Steelhead trout	adult	6°C	March 31, 2003	January 29, 2004 supportive	P0031
AQUIS-01-EFF-02	Rainbow trout	subadult adult	8 and 15°C	January 20, 2004 November 10, 2004	November 12, 2004 pivotal	P0052 P0088 - FOI
AQUIS-01-EFF.2-06	Chinook salmon	fingerling subadult	5 and 13°C	October 02, 2003 November 09, 2004	July 30, 2004 supportive	P0042 P0087 - FOI
AQUIS-01-EFF.2-14	Chinook salmon	fry juvenile	13°C	May 10, 2005	response pending	
AQUIS-01-EFF.2-15	Kokanee salmon	fingerling	10 and 15°C	September 22, 2005	response pending	
AQUIS-01-EFF.2-16	Chinook salmon	fingerling	10 and 15°C	May 27, 2005	response pending	
AQUIS-01-EFF.2-19	Kokanee salmon	juvenile	11 and 16°C	September 23, 2005	response pending	
AQUIS-01-SUPP-EFF-01	Rainbow trout Lake trout	subadult	9°C	May 08, 2003	January 29, 2004 supportive	P0034
AQUIS-01-SUPP-EFF-02	Yellowstone Cutthroat trout	adult	8°C	May 09, 2003	January 29, 2004 supportive	P0035
AQUIS-01-SUPP-EFF-03	Bull trout	subadult	9°C	May 14, 2003	January 29, 2004 supportive	P0036
AQUIS-01-SUPP-EFF-06	Chinook salmon	fry	7°C	May 26, 2005	response pending	
AQUIS-01-SUPP-EFF-07[a]	Rainbow trout	fingerling	12°C	April 20, 2005	response pending	

[a] Groups vs. Individual study, FSR titled "Efficacy of the Anesthetic AQUI-S® on Individually Sedated and Group-sedated Fingerling Rainbow Trout"

DRAFT LABEL CLAIM FOR USE OF AQUI-S® ON ALL FRESHWATER SALMONIDS

DRAFT

LEFT PANEL

HUMAN WARNING

- Keep out of reach of children.
- For animal treatments only.

EMERGENCY FIRST AID

- In case of contact, immediately irrigate eyes with plenty of water for at least 10 minutes. If irritation persists due to prolonged or excessive contact, seek medical advice.
- If large quantities are inhaled, move to fresh air at once.
- If swallowed, rinse mouth with water; give up to two glasses of water or milk. Seek medical advice immediately.

ADVICE TO DOCTOR: None

INHALATION (Breathing):

- Does not present an inhalation hazard under normal usage as the liquid has a low vapor pressure at ambient temperature.

INGESTION (Swallowing):

- Do not swallow; harmful if concentrated product is swallowed. If swallowed do NOT induce vomiting.

EYE CONTACT:

- Do not get in eyes; causes irritation. If splashed in eyes, irrigate immediately with copious amounts of water.

SKIN CONTACT:

- Avoid prolonged or excessive exposure; may cause irritation.

HUMAN PRECAUTIONS:

- Protective gloves are recommended to avoid excessive skin contact.
- Smell is minimal, but use in adequately ventilated area.
- Keep container tightly closed when not in use.
- Keep out of reach of children.

ENVIRONMENTAL PRECAUTIONS:

- Small spills can be wiped up with cloth or paper. Standard absorbents (sand, sawdust, vermiculite, etc) can be used to contain large spills.
- Wash area with water after wiping up with cloth or paper, or sweeping up absorbent.
- In case of fire, use foam, carbon dioxide, or dry chemical extinguishers. This product is not very flammable but toxic vapors may be released during fire.

STORAGE:

- Keep away from heat - store below room temperature (30°C).
- Store in tightly closed container.
- Store in a cool, dry area, away from direct sunlight.
- No special transport requirements necessary.

FOR CHEMICAL EMERGENCY SPILL, LEAK, FIRE, EXPOSURE, OR ACCIDENT
CALL CHEMTREC, DAY OR NIGHT
1-800-424-9300

DRAFT

Lot Number: ~~Expiration Date:~~ Date ~~Received:~~

DRAFT LABEL CLAIM FOR USE OF AQUI-S® ON ALL FRESHWATER SALMONIDS

DRAFT

MIDDLE PANEL

AQUI-S®

ANESTHETIC TO SEDATE ALL FRESHWATER SALMONIDS TO THE HANDLEABLE STAGE OF ANESTHESIA

ACTIVE INGREDIENT

Isoeugenol

GUARANTEED ANALYSIS:

Isoeugenol ..... 54% (w/w)

Adjuvant .....

READ ENTIRE PACKAGE INSERT BEFORE USING THIS PRODUCT

KEEP OUT OF REACH OF CHILDREN

Net Contents: mL or L

MANUFACTURED BY:

AQUI-S NEW ZEALAND LIMITED LTD

LOWER HUTT, NEW ZEALAND

NADA NO. xx-xxx , APPROVED BY FDA

DRAFT

DRAFT LABEL CLAIM FOR USE OF AQUI-S® ON ALL FRESHWATER SALMONIDS

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RIGHT PANEL

FOR ALL FRESHWATER SALMONIDS

INDICATIONS: To sedate all freshwater salmonids to the handleable stage of anesthesia

DIRECTIONS FOR USE: Expose fish to AQUI-S® at a rate of 20 to 60 milligrams AQUI-S® (10 to 30 milligrams isoeugenol) per liter [mg/L; equivalent to parts per million (ppm)] in a static bath until the desired level of sedation has been achieved.

Prior to use, dilute anesthetic based on AQUI-S® being 100% active ingredient.

Approximate time for freshwater salmonids to become, and recover from, handleable when treated with 20, 40, or 60 mg/L AQUI-S®

Target dose (mg/L)	Approximate median time to handleable	Approximate median time to recover from handleable
20	9.5 minutes (range, 2.5 - 30 min)	4.2 minutes (range, 1.1 - 8.8 min)
40	2.7 minutes (range, 1.1 - 6.2 min)	4.2 minutes (range, 1.8 - 6.5 min)
60	1.6 minutes (range, 1.0 - 3.0 min)	4.1 minutes (range, 1.5 - 7.1 min)

The amount of AQUI-S® required for sedation is dependant on the volume of water treated. Once the volume of water to be treated has been determined, use the following formula to determine the correct quantity of AQUI-S® required for treatment:

target concentration (mg/L) x treatment volume (gal) x 0.00378 = X.xx g AQUI-S®

Example calculation:

40 mg/L x 50 gal x 0.00378 = 7.56 g AQUI-S®

Use the following procedures to prepare working solutions of AQUI-S®:

- Measure AQUI-S® into a screw-cap or other sealable container.
- Dilute AQUI-S® at least 10-fold with water and shake vigorously to disperse AQUI-S® and form a stock solution.
- Add sufficient stock solution to tub/bucket of water to achieve the desired concentration of AQUI-S®.

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RIGHT PANEL (continued)

FOR ALL FRESHWATER SALMONIDS

LIMITATIONS AND CAUTIONS

- Handle animals gently. Avoid stress prior to treatment.
- Do not expose animals to direct sunlight or wind.
- Shake AQUI-S® container prior to use.
- If necessary, aerate AQUI-S® working solution with air to maintain dissolved oxygen concentration.
- To facilitate recovery, place sedated fish in clean well aerated water.
- To avoid overexposing fish to AQUI-S®, sedate only a few fish at a time. As you gain more experience working with AQUI-S®, more fish may be sedated at one time.
- In the event of overdosing or overexposure, remove fish immediately from AQUI-S® solution and irrigate gills with clean, well oxygenated water.
- Take into consideration life-stage and temperature of AQUI-S® solution when sedating fish to handleable.
- Avoid feeding fish before sedation.
- Due to the viscosity of AQUI-S®, care should be taken when diluting with cold water to ensure that AQUI-S® is properly mixed in the stock solution.
- Temperature and pH of the AQUI-S® working solution should be reasonably close to the temperature and pH to which the fish have been acclimated.

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