DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

I-011370-P-0049–TS

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

Re: Target Animal Safety technical section complete

Dear Dr. Erdahl:

Based upon the information you submitted on February 19, 2013, and the information contained in the investigational new animal drug file 011370, we consider the Target Animal Safety technical section to be complete. The technical section is complete for the use of emamectin medicated feed in freshwater-reared salmonids when administered at a dose of 50 mcg emamectin/kg BW/day for 7 consecutive days.

TARGET ANIMAL SAFETY
This technical section complete letter represents our finding that the studies and other information 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.

ALL OTHER INFORMATION
You did not address the All Other Information (AOI) technical section in this submission. Please include any information that becomes available in the AOI technical section.

FREEDOM OF INFORMATION (FOI) SUMMARY
We appreciate your cooperation in including the relevant portions of the FOI Summary with this submission. We have revised the Target Animal Safety section of the FOI Summary and a copy is enclosed. Please review the FOI Summary for accuracy and notify us if you find errors.

GENERAL COMMENTS
1. For the medicated feeds, the protocol states that the study feeds will be acceptable if the emamectin concentration is within 20% of the target concentration (Section 11.1). The protocol also states that the assay results from the homogeneity samples will be used to verify that the emamectin concentration is within an acceptable range (Section 11.2.1). Protocol section 11.1 states that if the emamectin concentration is outside the acceptable range, the sample will be re-analyzed and if the emamectin concentration is still out of range a new medicated feed batch will be made. The emamectin analyses were not conducted until after the in-life portion of the study was completed and revealed that one value was outside the acceptable range. If the

timing of the feed analyses were known prior to the start of the study, the protocol should have been amended because conducting the analyses after the in-life portion of the study left no opportunity to prepare a new batch of feed. Since the protocol was not amended, a deviation should have been prepared. Please ensure that all changes to or deviations from study protocols are properly recorded in future studies.

2. The raw data (histology scoring data capture forms and electronic copy of that raw data) show that anterior kidney was not examined in one fish (Tank 3, Slide No. 17) and spleen was not examined in one fish (Tank 3, Slide No. 11). The necropsy raw data indicate that these organs appeared normal and were therefore present. The histopathologist did not request recuts for either fish to obtain slides with the tissues. The tissues should have been examined, particularly the splenic tissue since this tissue was examined in only two fish per tank. The omission should have been reported as a deviation.

3. In the histopathological findings for the liver, the pattern of severity and the incidence of degeneration and necrosis observed in the study fish were somewhat similar to the pattern of severity of the glycogen vacuolation and may be related to cell damage or death associated with more significant vacuolation. The degree of vacuolation was considered marked or severe in ~50-60% of each group examined, in both reference and treated groups, warranting a discussion of the findings. The final study report (FSR) should have explained why the study fish were considered healthy despite the histopathological findings for the liver, particularly at the start of the study. You should have addressed the potential etiology of the degeneration, necrosis, and glycogen vacuolation and implications of the findings. We considered the fish healthy and appropriate for the study because the grossly visible lesions and histopathological changes in the liver can be seen in cultured populations of fish with normal growth.

4. Nephrocalcinosis was seen in several groups of study fish including fish collected prior to the study and fish collected at the end of the study. While the histopathological observations of the kidney tissue were equivalent across all the groups examined, and are therefore not indicative of a toxic effect of the emamectin, the FSR should have discussed the potential etiology and implications of the findings. Nephrocalcinosis has been observed in intensively reared salmonids. Published descriptions began to appear in the literature in the late 1960s. Many potential causes or associations have been investigated. We considered the fish healthy and appropriate for the study because the histopathological changes in the kidney can be seen in cultured populations of fish with normal growth. In addition, the nephrocalcinosis in this study was not associated with clinical signs of illness and lesions were not grossly visible during necropsy.

5. Decreased appetite was seen in the 3X treatment group. You should have interpreted this as an early sign of toxicity based on reported toxic syndromes associated with other macrocyclic lactones, which primarily cause neurotoxicity with clinical signs such as inappetance, ataxia, altered mentation, lethargy, seizure, and death, as no other cause was apparent. We consider this important information and included it in the results section of the FOI Summary. The study does demonstrate a margin of safety with regard to the appetite since the 2X group was unaffected.

6. The FSR includes several errors in the units used to report findings for the preparation and analysis of the study feeds. In the medicated feed preparation description in the FSR (p. 13), the units for the nominal emamectin concentration in

the medicated feeds are reported as grams emamectin per kilogram of feed (g/kg feed). In the results section of the FSR (p. 30), the units for the nominal emamectin concentration in the medicated feeds is stated as micrograms emamectin per kilogram of feed (mcg/kg feed). The correct units for these numeric values is milligram emamectin per kilogram of feed (mg/kg feed) as reported later in the FSR (p. 31). In addition, the medicated feed preparation description in the FSR (p. 13) states that 3.12, 6.26, and 9.37 grams of emamectin were added to 5 kg of feed to prepare the medicated feeds. Form 23 in the raw data provides the same amounts as grams of SLICE added to the five kilograms of feed. The correct values, the amount of SLICE in grams added for each 5 kg batch of feed, were stated on Form 23. In future study reports, please ensure that units are reported correctly for drug concentrations and drug doses and for drug products such as SLICE versus active pharmaceutical ingredients such as emamectin.

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 Section of the Freedom of Information Summary: Target Animal Safety