DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

INAD 4000 H-0091

David Erdahl, Ph.D.
National INAD Coordinator
USFWS Fish Technology Center
4050 Bridger Canyon Road
Bozeman, Montana 59715

JUN 10 2002

Dear Dr. Erdahl:

We refer to your submission dated January 3, 2002, to your investigational new animal drug (INAD) file for chloramine-T. You requested review of a study completed to demonstrate that a chloramine-T target dose can be achieved and maintained using a "charged" flow-through treatment method.

Based on information in this submission, the Division of Therapeutic Drugs for Food Animals considers the EFFECTIVENESS technical section complete for the purpose of recommending approval of a New Animal Drug Application for the use of chloramine-T as static **and** flow-through bath.

A final decision on the approval of the application will be made when all the data for all technical sections are viewed as a whole and it is determined that:

1) the information contained in and referenced by the application supports approval;

2) the GMP status of each manufacturing facility is current and satisfactory;

3) if a claim for categorical exclusion was made, conditions for the categorical exclusion are still applicable.

4) there is no new information that would preclude the approval of the application.

In addition, we have the following comments.

1. We found an error in your electronic data set for sample site R from raceway 6, replicate 2, at time 30 minutes. The electronic data set value was 10.7, not 11.1 as presented in Appendix F. Tables 3 (dosing trial #4) and 4 (a: middle of raceway, b: bottom of raceway; c: right-hand side of raceway) should be corrected and resubmitted to the file. We corrected the value during our verification of your methods.

2. In Table 5 (page 30), the percentages reported as differences from the means should be negative for those values less than the overall means. You reported all differences as positive percentages from the mean values. Also, for trial 4, time=0, QC#3, the value should read –1.0%, not 7.8% as presented. A corrected table should be submitted to the file.

3. We were able to verify your hypotheses tests for each time period using one-sample t-tests in SAS. To explore any potential sources of variation among sampling sites, we analyzed the data using repeated measures, mixed model methods including the fixed effects of strata (head, middle, tail), row (surface, middle, bottom), column (left, center, right), time, and all two-, three-, and four-way interactions, and the random effect of sample within trial. The covariance structure for the repeated measures was heterogeneous, first-order autoregressive (ARH(1)). Non-significant interaction terms were dropped from the model, starting with the highest order interaction terms, until only the significant interactions remained ($p < .05$). The reduced model contained the significant fixed effects of strata, time, and strata by time ($p < .005$). The graph of the least-squares means for strata by time interactions are presented in Appendix 1.

4. Based on our analyses, the highest concentration of chloramine-T was measured at the head of the raceway at time 0 and the lowest concentration was measured at the head of the raceway at 60 minutes, among all of the strata measured. Measured concentrations of chloramine-T were lower than the target of 12 mg/L at the middle and tail of the raceway at all time periods; however, the concentrations were within the 25% margin. Measured concentrations of chloramine-T at the tail of the raceway were more consistent over the 60 minute time period than were concentrations measured either at the head or middle of the raceway.

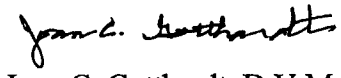
5. We suggest that the graph enclosed as Appendix 1 be included in the Freedom of Information Summary.

6. Two copies of the study were submitted. The study protocol was not included in the submission. For future submissions, the study protocol should be included in the final study report and each submission should include three complete copies of the materials.

Future correspondence regarding this submission to the files for your INAD exemption should be identified by the date of the submission and our file number, INAD 4000 H-0091, and be addressed to the Document Control Unit, HFV-199. Please include only one request per submission, clearly stating the request in the first paragraph of the submission.

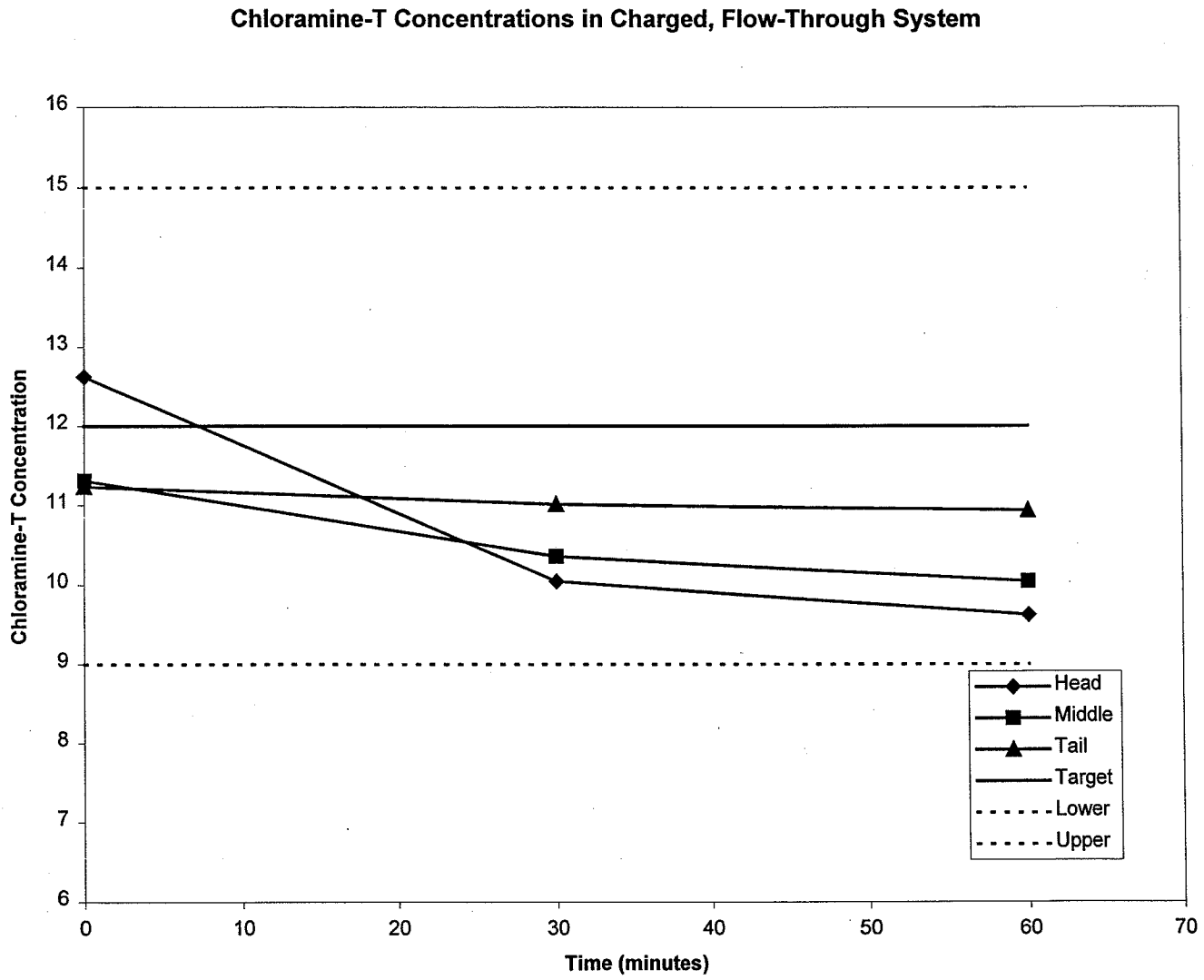
If you have any questions or comments regarding this correspondence, please telephone Dr. Susan Storey, Aquaculture Drugs Team at 301-827-7581.

Sincerely yours,



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

Enclosure

Appendix 1

Least-squares means for the strata by time interactions from the repeated measures, mixed model methods.