DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
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April 17, 2017

Re: Animal Welfare Assurance
#A4294-01 (OLAW Case D)

Dr. Steven M. Musser
Deputy Director for Scientific Operations
Food and Drug Administration
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD 20740

Dear Dr. Musser,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your April 10, 2017 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at FDA Center for Food Safety and Applied Nutrition. According to the information provided, OLAW understands that mice on a Listeria study lost between 10% and 31% of their body weight. Although the protocol listed weight loss as a sign of illness, no limit was set. The protocol did state that animals would be monitored during the study but this did not occur until the end. The Principal Investigator stated that distressed mice were euthanized, some mice showed adverse symptoms such as spinning, and some were found dead but none were examined by the Attending Veterinarian.

The corrective actions consisted of notifying the Principal Investigator (PI) about the noncompliance, creating an institutional policy on body weight loss in study animals whereby a loss of 10% must be reported to the veterinary staff, having PIs monitor weights throughout the study, having studies with weight loss monitored by a post approval monitor (PAM), amending the protocol form to reflect the weight loss policy, and having the veterinary staff perform daily health checks on study animals. The study in question has ended, but future animal work by this PI will be performed under enhanced oversight by the PAM or an individual designated by the Institutional Animal Care and Use Committee.

Based on the information provided, OLAW is satisfied that appropriate actions have been taken to investigate, correct, and prevent recurrence of the noncompliance. We appreciate having been informed about this matter and find no cause for further action by this Office.

Sincerely,

Axel Wolff, MS, D

Axel Wolff, M.S., D.V.M.
Director
Division of Compliance Oversight

cc: IACUC Chair

A4294-D

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY & APPLIED NUTRITION

APR 10 2017

Axel V. Wolff, DVM
Director, Division of Compliance Oversight
MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892

Re: Assurance A4294-01 - Non-compliance to protocol

Dear Dr. Wolff:

The U.S. Food and Drug Administration's Center for Food Safety and Applied Nutrition (CFSAN), is conducting research on *Listeria*. In this study, 29 mice experienced a greater than 10% loss of body weight. Of those 29 mice, 8 had a greater than 20% loss of body weight, and one mouse experienced a 31% loss of body weight. In the protocol, under the section titled "resultant effects that the animals are expected to experience," weight loss was listed as a sign of illness; although there was no specific limit indicated for the percent body weight loss that would require attention. However, the section of the protocol titled "experimental endpoint criteria" states that "animals will be screened for body weight", which to the CFSAN Institutional Animal Care and Use Committee (IACUC), suggests that the study animals will be monitored during the course of study.

At the request of the CFSAN IACUC, the chairperson originally contacted the Office Laboratory Animal Welfare (OLAW) on February 21, 2017 and spoke to Dr. Axel Wolff on February 22, 2017 regarding the significant weight loss in the mice that was not reported. At this point, the failure to report the study animals' significant weight loss was not deemed to be a protocol non-compliance issue by OLAW because no specific limit on body weight loss had been established in the protocol. However, Dr. Wolff was concerned about the humane aspects of the weight loss.

During an investigation into the issue, the Principal Investigator (PI) stated that the mice that appeared to be distressed were euthanized. According to the study records, some mice displayed

U.S. Food & Drug Administration
Center for Food Safety & Applied Nutrition
5001 Campus Drive
College Park, MD 20740

other adverse symptoms, such as spinning. Additionally, some mice were found dead. At this point during the study, the mice were not physically examined by the attending veterinarian.

On March 2, 2017, the IACUC Chairperson met with the PI to discuss the study animal weight loss issue. During this meeting the Chairperson learned that the PI only determined the significant percent body weight loss at the end of the study and did not monitor the weight loss during the course of the study, as suggested under the experimental endpoint criteria.

During the March 21, 2017, IACUC meeting, the details of the disclosure were discussed and the committee decided that this was a protocol non-compliance issue that must be reported to the Office of Laboratory Animal Welfare.

On March 24, 2017, the IACUC Chairperson and Dr. Wolff discussed the disclosure from the PI that the PI did not monitor weight loss until the end of the study. At this point Dr. Wolff indicated that this particular incident was a non-compliance violation of the study protocol, especially since significant body weight was lost by the study animals.

This document is the final record of events that was requested by the Office of Laboratory Animal Welfare.

FDA's response to address the protocol non-compliance issues is as follows:

1. A letter was sent to the PI describing the non-compliance issues related to the protocol. The animal study portion of the protocol is complete; however, should any further animal study be conducted on this protocol it will be monitored by the Post Approval Monitor (PAM).

2. CFSAN has developed a policy on body weight loss in study animals. In the policy, a greater than 10% loss of body weight in a study animal must be reported to the veterinary staff. The policy also indicates that if body weight loss is listed under either the "resultant effects that the animals are expected to experience" section or the "experimental endpoint criteria" section of the study protocol, the PI must monitor each

study animal's weight throughout the entire course of the study. Adherence to the weight monitoring requirement will be monitored by the PAM.

3. The CFSAN animal study protocol form (Animal Study Protocol Form ASP01) will be amended to clearly reflect the CFSAN study animal weight loss policy. These changes will occur under the "resultant effects that the animals are expected to experience" section of the protocol form and the "experimental endpoint criteria" section of the protocol form. Adherence to the requirement for monitoring the weight of each study animal throughout the entire course of the study will be monitored by the PAM.

4. The animal study portion of the protocol is complete; however, should any further animal work be conducted on this study protocol it will be monitored by the PAM or an IACUC designated person. Any future animal studies that the PI plans to perform at CFSAN, which require body weight monitoring, will be monitored by the PAM or an IACUC designated person.

5. The veterinary staff will perform daily physical health checks on all study animals, including those dosed with an infectious agent.

6. Due to the nature of this incident, and repeated protocol non-compliance issues on this animal study protocol, any future animal work on a CFSAN study protocol by the PI will be monitored by the PAM or an IACUC designated person. The enhanced monitoring of the PI by the PAM will continue until the IACUC is completely satisfied with the conduct of animal work on any CFSAN approved animal study protocol.

The FDA Center for Food Safety and Applied Nutrition is committed to protecting the welfare of animals used in research and greatly appreciates the guidance and assistance provided by the Office of Laboratory Animal Welfare in this regard. Should you have any questions regarding this report, please contact (b) (6) via e-mail (b) (6) @fda.hhs.gov) or telephone (b) (6)

Sincerely,

Steven Musser, Ph.D.
Deputy Director for Scientific Operations
Center for Food Safety
and Applied Nutrition

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Tuesday, April 11, 2017 1:36 PM
To: (b) (6)
Subject: RE: Incident Report Assurance A4294-01

Thank you for this report, Dr. (b) (6) I will respond soon. It is not necessary to submit an additional hard copy.

Axel Wolff, M.S., D.V.M.
Director, Division of Compliance Oversight
OLAW

From: (b) (6) [mailto: (b) (6) @fda.hhs.gov]
Sent: Tuesday, April 11, 2017 12:57 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: Incident Report Assurance A4294-01

Good afternoon Dr. Wolff,

Attached is the non-compliance incident report for FDA/CFSAN Assurance A4294-01. The original shall be sent to the Bethesda Address.

Thank you for your help. We greatly appreciate your guidance and assistance.

Sincerely,
(b) (6)

(b) (6)
Research Biologist, Division of Applied Regulatory Toxicology

CFSAN/OARSA/DART
U.S. Food and Drug Administration
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