DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, Maryland 20892-6910
Home Page: http://grants.nih.gov/grants/olaw/olaw.htm

FOR EXPRESS MAIL:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 402-7065

November 14, 2019

Re: Animal Welfare Assurance
#A3237-01 (OLAW Case 2Z)

Ms. Steffani Webb
Vice Chancellor for Administration
Institutional Official
University of Kansas Medical Center
3901 Rainbow Road, MS 2015
Kansas City, KS 66160

Dear Ms. Webb,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your October 14, 2019 letter that was provided in response to our October 2, 2019 correspondence requesting additional information regarding the reported adverse event involving mice hindpaw injuries after injections with a compound with pH of approximately 12 at the University of Kansas Medical Center.

Your response described corrective actions that included the laboratory establishing a consultation procedure to assure biocompatibility of the compound prior to any future experiments. An appropriate biochemist/chemist/toxicologist will be consulted to assure that the compound is reconstituted at a pH that is appropriate for administration. For future substances, prior to administration, the lab will follow established, published formulas to assure biocompatibility of substances, or the lab will consult with individuals with expertise to assure the appropriateness of compounds for administration.

Clarification was provided regarding the existing IACUC policy on the use of Non-pharmaceutical grade compounds that addresses the need for determining safe, biocompatible substances prior to administration. Also, the protocol includes a specific section for scientific reasoning for use and possible toxicity/hazard information, and the IACUC has a board-certified toxicologist for a consultant, if necessary. The IACUC policy on the use of Non-pharmaceutical grade compounds was reviewed, and it was noted that additional guidance for the research community was warranted. The IACUC will review a revised policy that includes information regarding the need for use of established, published formulas and consultation with appropriate experts for new compounds and formulations. Once the new policy is reviewed and approved by the IACUC, the research community will be informed, and additional training will be provided through lunch and learn sessions and through the Post-Approval Monitor. Document review by the Post-Approval Monitor will continue related to the use of non-pharmaceutical grade compounds to assure compliance with the revised policy.

Thank you for providing the additional information and for the efforts taken to further address this incident. We appreciate your commitment to the Public Health Service Policy on the Humane Care and Use of Laboratory Animals and to fulfilling the responsibilities of the institution and the IACUC. OLAW is satisfied that the described actions taken to prevent recurrence are appropriate and find no cause for further action by this Office.

Obtained by Rise for Animals.
Uploaded to Animal Research Laboratory Overview (ARLO) on 09/15/2020

Sincerely,

(b) (6)

Jane Na, DVM, CPIA
Veterinary Medical Officer, OLAW
National Institutes of Health

cc: IACUC Contact

Obtained by Rise for Animals.
Uploaded to Animal Research Laboratory Overview (ARLO) on 09/15/2020

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, Maryland 20892-6910
Home Page: http://grants.nih.gov/grants/olaw/olaw.htm

FOR EXPRESS MAIL:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 402-7065

October 2, 2019

Re: Animal Welfare Assurance
#A3237-01 (OLAW Case 2Z)

Ms. Steffani Webb
Vice Chancellor for Administration
Institutional Official
University of Kansas Medical Center
3901 Rainbow Road, MS 2015
Kansas City, KS 66160

Dear Ms. Webb,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your July 10, 2019 letter reporting an adverse event at the University of Kansas Medical Center. According to the information provided, OLAW understands that on June 3, 2019, hind paw injections in ten mice unexpectedly caused acute swelling and ultimately blistering with some affected paws showing apparent necrosis. The animals were removed from the study and were euthanized. The laboratory determined that the pH of the prepared material was approximately 12. The letter indicated that the associated animal work was funded by a National Institutes of Health grant.

Corrective action described in the letter indicated that a protocol addendum was submitted to adjust the dose due to difficulty adjusting the substance to a neutral pH for the concentration and volume to be administered.

Although the letter indicates that this incident was an unexpected adverse event, this may be more accurately described as a noncompliance with the Public Health Service (PHS) Policy on the Humane Care and Use of Laboratory Animals (Policy) with failure to appropriately minimize animal pain and distress and potentially a deviation from provisions of the *Guide for the Care and Use of Laboratory Animals*. It is unclear if the University of Kansas Medical Center has a policy or guidance regarding administration of substances to animals including the concepts of ensuring the biocompatibility of substances. Page 31 of the *Guide for the Care and Use of Laboratory Animals* indicates that during IACUC protocol review, "consideration should be given to the grade, purity, sterility, pH, pyrogenicity, osmolality, stability, site and route of administration, formulation, compatibility, and pharmacokinetics of the chemical or substance to be administered, as well as animal welfare and scientific issues relating to its use (NIH 2008)." Please indicate how the IACUC considers the suitability of substances administered to animals during protocol review and how researchers are educated regarding this concept in order to appropriately minimize animal pain and distress.

Please provide a response **no later than November 4, 2019** by email to jane.na@nih.gov and describe additional corrective measures that may have been or that will be instituted as well as a timeline or schedule of implementation, if applicable. We appreciate your attention to these matters and look forward to your response.

Obtained by Rise for Animals.
Uploaded to Animal Research Laboratory Overview (ARLO) on 09/15/2020

Sincerely,

(b) (6)

Jane Na, DVM, CPIA
Veterinary Medical Officer, OLAW
National Institutes of Health

cc: IACUC Contact

Obtained by Rise for Animals.
Uploaded to Animal Research Laboratory Overview (ARLO) on 09/15/2020

A3237-22

KU MEDICAL CENTER
The University of Kansas

July 10, 2019

Axel Wolff, MS, DVM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive – MSC 7982
Bethesda, MD 20892-7982

Regarding: **University of Kansas Medical Center -- Assurance #A3237-01**

Research Project: **Animal Models of Peripheral Neuropathy**
IACUC Number: 2019-2492

Funding Agency: **NIH-NINDS R01-NS043314**

Dear Dr. Wolff:

In accordance with PHS Policy IV.F.3, the University of Kansas Medical Center (KUMC) Institutional Animal Care and Use Committee (IACUC) is reporting an adverse event.

On June 3, 2019, 10 mice received dorsal hindpaw injections of β-hydroxybutyrate (BHB) as part of an approved set of experiments to begin studying the potential neuroprotective effects of ketone bodies. Unexpectedly, upon receiving the injections, mice vocalized and attended to the injection site. Additionally, the injected feet became swollen after 2 hours, but returned to normal by 24 hours post-injection. However, at 48 hours post injections, blistering and, in some cases, apparent necrosis had occurred, and the mice were removed from study and euthanized.

Specific Corrective Action:

After further investigation, laboratory staff determined that the pH of the prepared BHB reconstituted to deliver 250mg/kg of BHB in a 20 µl volume as originally approved, was ~12. Because of difficulties adjusting BHB to a neutral pH at the originally proposed concentration in the desired volume of 20µl, an addendum was approved on 6/21/19 to repeat the study at a reduced dose of 5mg/kg.

Office of the Executive Vice Chancellor
3901 Rainbow Blvd. | Mail Stop 2015 | Kansas City, KS 66160 | (913) 588-1440 | FAX (913) 588-1412 | www.kumc.edu
Obtained by Rise for Animals.
Uploaded to Animal Research Laboratory Overview (ARLO) on 09/15/2020

IACUC and RABS Action:

This information was presented to the convened IACUC on June 18, 2019. Following discussion, the IACUC determined the adverse event was appropriately resolved and further voted unanimously to report this incident to the relevant regulatory and accrediting agencies. This information is also being provided to the Association for the Accreditation of Laboratory Animal Care (AAALAC).

It is important to note that Research Staff promptly contacted RABs after initial observations on June 3 and again 2 days later when animals were removed from study. RABS will continue to stress the importance of maintaining good communication with LAR staff and the IACUC when unexpected outcomes occur. Procedures for adverse event reporting is a required component of training for all new animal users at KUMC. Additional avenues of training include research department meetings, Post-Approval Monitoring reviews and/or additional communications through signage and quarterly newsletters. If you have questions or need more information, please feel free to contact me at (b) (6)

Sincerely,

(b) (6)

Steffani Webb
Vice Chancellor for Administration

cc: (b) (6)
Nathan Culley, DVM, DACLAM, Chair, IACUC
Douglas Brandt, DVM, Executive Director, Laboratory Animal Sciences, Attending Veterinarian

Obtained by Rise for Animals.
Uploaded to Animal Research Laboratory Overview (ARLO) on 09/15/2020

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Friday, July 12, 2019 10:42 AM
To: Nathan Culley
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Incident Report for the University of Kansas Medical Center A3237-01

Thank you for these reports, Dr. Culley. We will send responses soon.
Axel Wolff

From: Nathan Culley <nculley@kumc.edu>
Sent: Friday, July 12, 2019 9:59 AM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: Incident Report for the University of Kansas Medical Center A3237-01

Dr. Wolff,

Please find attached, three (3) animal welfare compliance report letters from the University of Kansas Medical Center (A3237-01). One report is a little delayed due to our AAALAC site visit in June, I apologize for that. Please let me know if you have any further questions regarding the reports.

Regards,

Nathan C Culley, DVM, DACLAM
IACUC Chair
Executive Director, Regulatory Affairs for Biological Sciences
University of Kansas Medical Center
nculley@kumc.edu
(b) (6)

Obtained by Rise for Animals.
Uploaded to Animal Research Laboratory Overview (ARLO) on 09/15/2020