DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
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February 21, 2017

Re: Animal Welfare Assurance
#A4300-01 [OLAW Case C]

Dr. Peter Marks
Director, Center for Biologics and Research
FDA - Center for Biologics Evaluation & Research
10903 New Hampshire Avenue, Bldg. 71
Silver Spring, MD 20993

Dear Dr. Marks,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your February 16, 2017 letter reporting three instances of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the FDA White Oak Consolidated Animal Program, following up on an initial telephone report on February 15, 2017. According to the information provided, OLAW understands the following about the incidents and the corresponding corrective actions:

1) Mice were being tail snipped after 21 days of age although this was not described in the approved protocol. The institutional guidelines on rodent genotyping were not clear regarding the need for scientific justification when the procedure is performed on mice over 21 days old.

Corrective action: The genotyping guidelines were updated and staff was trained on them. Some protocols were amended to allow performance of tail snips after 21 days of age under anesthesia.

2) Several mice were moved to a laboratory for experimental procedures and euthanasia by cervical dislocation although neither the performance site or euthanasia method were described in the protocol.

Corrective action: The protocol was amended to include the procedure and performance site.

3) Eight live mouse pups were found in a disposal bag due to a failure to verify death following exposure to CO2 for euthanasia.

Corrective action: The pups were appropriately euthanized, the Principal Investigator and laboratory staff were retrained on the proper conduct of euthanasia, the protocol was amended to include a detailed description of pup euthanasia, and mouse pup euthanasia will be conducted by the facility staff until investigator training is completed.

Based on its assessment of these explanations, OLAW understands that measures have been implemented in each situation to correct and prevent recurrence of the problem. OLAW concurs with the actions taken by the institution to comply with the PHS Policy.

Sincerely,

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

cc: IACUC Chair

A4300

White Oak Consolidated Animal Program

Food and Drug Administration
10903 New Hampshire Ave. Bldg 71
Silver Spring, MD 20993

Date: February 16, 2017

From: (b) (6) DVM, Ph.D., and Chairperson
White Oak Consolidated IACUC

(b) (6)

Peter W. Marks -A

Digitally signed by Peter W. Marks -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Peter W. Marks -A, 0.9.2342.19200300.100.1.1=2000932716
Date: 2017.02.17 17:09:33 -05'00'

Through: Peter Marks, MD, Ph.D., and Institutional Official

Subject: Incident Report

To: Axel V. Wolff, MS, DVM, Director, Division of Compliance Oversight, OLAW, NIH

As a follow-up to our conversation regarding the two incidences we discussed on February 15, I am providing the details in this letter. Please note that one additional incident we did not discuss is also described. If you have any additional questions please feel free to contact me.

Incident 1

Veterinary staff discovered that work on two investigators' protocols included rodent genotyping by tail snip being performed after 21 days of age, inconsistent with what was approved in their protocols. The work was performed by breeding technicians using guidance and methods described in the *WOC ACUC Guideline for Genotyping Procedures in Mice and Rats*. Tail biopsies on mice older than 21 days were performed under isoflurane anesthesia; though the investigators requesting these procedures did not have mouse tail biopsy after 21 days of age described and scientifically justified on their protocols.

In reviewing the *WOC ACUC Guidelines for Genotyping Procedures in Mice and Rats*, it was found that a scientific justification to perform tail biopsy genotyping in rodents over 21 days of age was not clearly communicated.

Corrective Actions:

The *WOC ACUC Guidelines for Genotyping Procedures in Mice and Rats* was immediately updated to provide clear information regarding the requirement for justification in the ASP of tail biopsy genotyping in rodents after 21 days of age. When possible, this procedure is routinely performed on pre-weanling mice. Alternative methods including ear punches are also utilized when practical. The affected research labs have been notified, and DVS technicians, the contract staff, and animal researchers will be trained on the updated guideline. Several labs clarified language in their protocol, gaining IACUC approval to perform tail biopsy under isoflurane anesthesia after 21 days of age. Whenever possible, tail biopsy genotype procedures are to be performed on pre-weanling mice.

The finding and correction will be shared with all users at the next quarterly animal users meeting in March, 2017, and a genotyping and rodent identification training webinar is planned for Spring 2017, and will be given by one of the DVS-approved rodent vendors.

White Oak Consolidated
Animal Program

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10903 New Hampshire Ave. Bldg 71
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Incident 2

One cage of mice on an approved protocol was moved from the Vivarium to the lab for experimental procedures followed by cervical dislocation. The use of this lab location and cervical dislocation by this employee were not listed on this particular approved protocol, though other protocols for the investigator do allow for transportation to the lab as well as cervical dislocation by this employee, who is known to be proficient.

Corrective Actions:
This protocol and possibly other protocols for this investigator will be amended to include these procedures and submitted for veterinary verification, review and approval.

Incident 3

A researcher was euthanizing adult mice and pups in a procedure room as an approved activity on their protocol. Later, an animal health technician (AHT) completing his daily assigned work at the end of the day removed the room medical pathological waste (MPW) garbage bag to replace with a fresh bag, and noted 8 moving pups that had been exposed to CO2 for euthanasia, along with dead adults in a carcass bag. He immediately removed the bag and contacted his supervisor and the facility veterinarian. Following their instructions, the AHT then exposed the pups to CO2 for another 30 minutes, followed by decapitation of the pups as a secondary euthanasia method. The researcher responsible for putting the live pups in the MPW bag explained that he usually uses a longer exposure CO2 Euthanex lid in a different procedure room for euthanasia of pups, and to his knowledge has never before had issue performing pup euthanasia.

Corrective Actions:

1. The Attending Veterinarian (AV) immediately contacted the Principal Investigator (PI) and laboratory associate involved in the incident and provided a link to the White Oak Animal Program (WOAP), IACUC-approved Euthanasia Guideline and explained the importance of prolonged CO2 exposure in order to appropriately euthanize neonatal mouse pups. In addition, it was made clear that it is appropriate to follow CO2 euthanasia of pups with an acceptable secondary method of euthanasia, such as decapitation that is described in the Guideline.
2. The PI is required to update their protocol to clearly describe the neonatal pup euthanasia steps they will use. This new information must be IACUC reviewed and approved.
3. Laboratory members will be trained on acceptable euthanasia procedures in mice including euthanasia of mouse neonates. This training will be documented, and documentation will be retained by the WOAP-IACUC.
4. Only after the above corrective actions are completed will the lab be allowed to euthanize neonatal mouse pups in the animal facility. Any neonatal mouse euthanasia that needs to be performed on their protocol prior to the completion of training will be done by DVS staff.

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Tuesday, February 21, 2017 7:55 AM
To: (b) (6)
Subject: RE: Incident Report for FDA White Oak Consolidated Animal Program Assurance A4300-01

Thank you for this report. We will respond soon.

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

From: (b) (6) [mailto (b) (6) @fda.hhs.gov]
Sent: Tuesday, February 21, 2017 7:28 AM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Dennis, John (FDA/CBER) <John.Dennis@fda.hhs.gov>; (b) (6) (FDA/CDER) (b) (6) @fda.hhs.gov>; Marks, Peter (FDA/CBER) <Peter.Marks@fda.hhs.gov>; (b) (6) (FDA/CBER) (b) (6) @fda.hhs.gov>
Subject: Incident Report for FDA White Oak Consolidated Animal Program Assurance A4300-01

The White Oak Consolidated (WOC) Animal Program and IACUC, is self-reporting a non-compliance incident and corrective action plan for Animal Welfare Assurance A4300-01. Please review the attached Incident Report.

Please contact Dr. John Dennis, (b) (6) or Dr. (b) (6) if you have any questions.

Kellie Werner-Moran
WOC IACUC Administrator
Division of Veterinary Services
(b) (6)

A4300-C

Office of Laboratory Animal Welfare

OLAW

Initial Report of Noncompliance

By: Qw

Date: 2/15/17 Time: 7:40

Name of Person reporting: (b) (6) IACUC chair
Telephone #: (b) (6)
Fax #:
Email:

Name of Institution: FDA / CDER
Assurance number: A4300

Did incident involve PHS funded activity? Yes
Funding component: _____
Was funding component contacted (if necessary): _____

What happened?
1) Trial surgeries done after 21 days old. Not on protocol, used isoflurane
2) Didn't list transport of mice to lab, didn't list cervical dislocation

Species involved:
Personnel involved:
Dates and times:
Animal deaths:

Projected plan and schedule for correction/prevention (if known): _____
1) make policies clearer
2) Amend protocol

Projected submission to OLAW of final report from Institutional Official:

OFFICE USE ONLY
Case # _____

Wolff, Axel (NIH/OD) [E]

From: (b) (6) @fda.hhs.gov>
Sent: Tuesday, February 14, 2017 11:44 AM
To: Wolff, Axel (NIH/OD) [E]
Subject: Possible OLAW reporting items

Hi Axel,

I am sorry I missed your call. I should be available between Noon – 1:30pm today and tomorrow morning from 7:30 - 10:45am. If any of these times works for you, please let me know when so that I can discuss these issues with you to determine if we need to officially report these items.

Kind Regards,
(b) (6)

(b) (6) DVM, Ph.D.
Research Veterinary Medical Officer
U.S. Food & Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
(b) (6)