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

July 22, 2019

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

Dr. Peter Marks
Director, Center for Biologics and Research
FDA – White Oak Consolidated Animal Program
10903 New Hampshire Avenue, Bldg. 71
Silver Spring, MD 20993

Dear Dr. Marks,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your July 16, 2019 letter reporting an instance 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 July 10, 2019. According to the information provided, OLAW understands that mice on a shigella study were found to be hunched and scruffy. The veterinarian examined them and directed that hydrogel be added to the cages. The laboratory staff was responsible for monitoring the mice twice daily to assess whether the clinical endpoints had been reached and the animals required euthanasia. Some mice were noted to be in worse clinical condition and the veterinarian contacted the laboratory staff to evaluate the mice but no one responded. Because some mice may recover, the mice were to be evaluated by the research staff. The next day seven mice had died and five were in critical condition.

The immediate action taken consisted of the Principal Investigator (PI) euthanizing the affected mice. The PI stated that the disease progression in this cohort of mice was later than expected. To prevent a recurrence the PI updated the protocol with contact numbers for all key personnel, ensured that all seriously ill animals are euthanized the same day by facility staff if laboratory staff has not done so, amended the protocol to clarify observation intervals and to indicate that more frequent observations are required as the disease advances, and clarified the protocol to clearly describe the clinical signs of the humane endpoints and to describe supportive therapy.

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

Sincerely,

Axel Wolff, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare

cc: IACUC Chair

AA306

FDA

White Oak Consolidated Animal Program

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

Date: 16 July 2019

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

Through: Peter Marks, MD, PhD, CBER Institutional Official Peter W. Marks -S

Digitally signed by Peter W. Marks -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Peter W. Marks -S, 0.9.2342.19200300.100.1.1=2000532716
Date: 2019.07.16 14:14:06 -04'00'

Subject: Incident Report

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

Details:

On Friday, May 10th, a group of mice (12 cages) infected with shigella was found to be sick due to study. Mice were hunched and scruffy. An email was sent in the morning to the lab staff to alert them. The PI responded by e-mail indicating that the mice were recently challenged, animals were expected to show signs of sickness and that the lab was responsible to monitor the mice twice a day to determine if they had reached humane endpoints before euthanizing them. Later that same day, the facility veterinarian recommended that hydrogel be added to all cages as support therapy, which the PI approved by phone. When providing the gel, the veterinarian noticed 2-3 mice that were in slightly worse condition than the rest of the group, with reduced response to stimuli but not moribund. An email was sent to the lab personnel listed in the animal protocol requesting their evaluation and was followed by phone calls. No response was received.

The basis for the veterinarian's decision to not euthanize these animals included the following: the protocol and PI's email indicated these mice were monitored by lab personnel twice daily and the PI had recently responded approving the request for support therapy, thus, there was an expectation that the lab staff would come to check these mice before the end of the day; this protocol involved vaccine evaluation and challenge studies with animals in category E, and these mice had not reached the protocol-defined endpoint for category E. According to the protocol, some sick animals might recover from the disease and thus, premature termination of these mice could have interfered with the goal of the study. On Saturday, May 11th, seven mice (including the mice mentioned in the email on Friday) were found dead and five mice were in critical condition. Technical staff contacted the PI and he came to euthanize the critical mice on the same morning.

The PI explained that this particular experiment was somehow atypical in that the peak of mortality occurred later than expected (around day six instead of day three or four post-inoculation). Because mortality had not been observed on the expected days, the investigator concluded that an error had occurred in the experiment and did not consider it necessary to continue monitoring these mice twice daily. He also apologized for not being responsive to phone call attempts on Friday afternoon.

Although the veterinary staff has institutional authority to use discretion in treating or euthanizing study animals without permission from investigators, in this category E study, disease progressed in a way not

expected by the investigator or by the animal care staff and veterinarian. The study had been designed and executed so that critically sick animals would not be expected on the weekend.

The incident was relayed by phone to OLAW on July 10, 2019.

Corrective Actions:

A number of corrective actions were discussed with some already implemented:

- The PI will update the protocol with cell phone numbers for all key personnel, instead of the minimum required after-hours emergency contacts (two).
- In the future, when seriously ill Shigella- infected animals are found, they will be euthanized by DVS by close of business day, if handling by the lab staff cannot be confirmed.
- The PI will amend the protocol and state that the frequency of observation of animals during the critical period will be modified to specify either approximate time of observations (one in the morning one in the afternoon after 2pm) or indicate that the two daily observations will be done at least 6-8 hours apart. In view of the present incident, the period of increased frequency of observation should also be extended to account for atypical experiments like this one. Additional monitoring (3 times a day) should be considered if disease progression is rapid and variable.
- Humane endpoints in the protocol include the following language: *If mice in any group are discovered that have (1) significant weight loss of 15% or more, (2) lost their ability to move and are unable to reach food and water, and (3) have lost their responsiveness to external stimuli, will be euthanized to alleviate further suffering.* Together with the veterinary staff, the investigator will revise or add additional humane endpoints that are specific to this model and the scientific objectives related to vaccine protection.
- Supportive therapy such as hydrogel or Nutra-gel is acceptable in these studies, and the protocol will be modified to include authorization of nutritional support for any mice that appear hunched or ill.

Our OLAW Assurance # is 4300-01.

Morse, Brent (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Thursday, July 18, 2019 11:19 AM
To: WO AP IACUC; OLAW Division of Compliance Oversight (NIH/OD)
Cc: Dennis, John (FDA/CBER); (b) (6) (FDA/CBER); Marks, Peter (FDA/CBER); (b) (6) (b) (6) (FDA/CBER)
Subject: RE: Incident Report for FDA White Oak Consolidated Animal Program Assurance # 4300-01

Thank you for providing this final report. We will send an official response soon.

Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

From: WO AP IACUC [mailto:WOAPIACUC@fda.hhs.gov]
Sent: Wednesday, July 17, 2019 8:49 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/CBER) (b) (6) @fda.hhs.gov>; Marks, Peter (FDA/CBER) <Peter.Marks@fda.hhs.gov>; WO AP IACUC <WOAPIACUC@fda.hhs.gov>; (b) (6) (b) (6) @fda.hhs.gov>; (b) (6) (FDA/CBER) (b) (6) @fda.hhs.gov>
Subject: Incident Report for FDA White Oak Consolidated Animal Program Assurance #4300-01

Good Morning,

The White Oak Consolidated (WOC) Animal Program and the IACUC, is self-reporting a non-compliance incident and corrective action plan for Animal Welfare Assurance #4300-01. Please review the attached Incident Report.

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

Thank you,
(b) (6) BS, LAT
Assistant IACUC Coordinator
WO AP IACUC

A4300-H

Office of Laboratory Animal Welfare

OLAW

Initial Report of Noncompliance

By: AW

Date: 7/10/19 Time: 2:00

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

Name of Institution: FDA WHITEOAK
Assurance number: A4300

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

What happened?

Mice on shigella study showed clinical signs + husbandry staff assumed PI would euthanize. Mice got sick + died.

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

Projected plan and schedule for correction/prevention (if known): _____

Advised he'd to have contact info available, train Caretakers

Projected submission to OLAW of final report from Institutional Official:

OFFICE USE ONLY
Case #_____