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

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March 15, 2018

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

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 March 14, 2018 letter reporting four related instances of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the FDA White Oak Consolidated Animal Program. According to the information provided, OLAW understands the following about the incidents and the corresponding corrective actions:

1) Fifty two additional mice were born than were approved on the protocol because the breeding pairs were not separated. The breeding scheme was not clearly described in the protocol and there was insufficient instruction from the laboratory staff to the technicians.

2) Surrogate dams were used to nurture pups whose mothers provided poor care and lactation. Pups from the surrogates were not counted which resulted in an excess of 841 animals not approved on the protocol. The breeding scheme was not clearly described in the protocol and there was insufficient instruction from the laboratory staff to the technicians.

3) Mice had inadvertently been placed on the wrong protocol and when they were transferred to the correct protocol there was an excess of 20% more animals than approved.

4) Mice being bred for cryopreservation were not closely tracked and the approved number was exceeded by 132 animals. In all instances, the investigators did not understand that all mouse pups were to be counted at seven days old, even if not retained for experimental use. Also there was a problem between the animal census database and the web interface used by the investigators which resulted in improper notifications of animal numbers. The breeding reports developed by the animal facility were not used by the laboratory staff which contributed to the incorrect tracking of animals and the excess numbers.

The corrective actions consisted of:

1) Amending all affected protocols to account for the excess animals.

2) Counseling the investigators on recordkeeping responsibilities and on maintaining colony numbers within the approved amount.

3) Having the Institutional Animal Care and Use Committee (IACUC) notify all investigators with breeding protocols to track animal numbers, providing breeding guidelines, and monitoring breeding activities during semi-annual inspections.

4) Having contract staff use the animal census database to monitor animal numbers and to notify the veterinarian and IACUC when 80% of the approved number has been reached. The IACUC will notify the investigator to take action to not exceed the approved number.

5) Upgrading the census database and web interface to make animal numbers available to investigators. Notifications will be sent out when 80% and 100% of the approved total have been reached. Work will be stopped or the protocol amended to avoid use of unapproved numbers of animals.

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 IACUC to comply with the PHS Policy.

Sincerely,

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

cc: IACUC Chair

A4300-F

White Oak Consolidated Animal Program

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

Date: March 14, 2018

From: (b) (6) DVM, PhD, 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=2000932716
Date: 2018.03.14 12:17:12 -04'00'

Subject: Incident Report, breeding protocol overages

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

Incident #1:

An investigator intended to breed mice from generations F0 through F5 followed by expansion of F5 offspring for experimental protocol use. This detail was not described in the approved protocol, but was verbally communicated to animal facility staff. Unfortunately, mice from generations F0 through F3 were not separated and breeding continued resulting in 52 offspring that were not needed nor approved to be bred.

Incident #2:

A breeding protocol included use of additional surrogate dams to help nurture young knockout mice, whose mothers exhibit poor lactation and poor maternal care. The investigator did not properly estimate and include pups from the surrogates as counting against their requested total mice in the experimental protocol. As a result, this investigator exceeded their approved animal numbers by 841 animals, or 50% of the approved number.

Incident #3:

An investigator had two animal protocols, one for breeding, the other for experiments. Due to a clerical error, approximately 159 breeding animals were added to the incorrect protocol. This error was identified during a review of breeding records by the animal facility. Once the animals were transferred to the correct protocol, it was discovered that the breeding protocol had exceeded the approved animal numbers by greater than 20%.

Incident #4:

An investigator planned to cryopreserve a strain of mice prior to ending breeding and closing out a protocol. Breeding of the strain to be cryopreserved continued while they obtained a contract with the outside vendor to complete the services. However, during this time the total animal numbers were not being closely monitored and the investigator exceeded the approved number of animals to be bred on the protocol by 132 animals, or 25% of the approved number.

White Oak Consolidated
Animal Program

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

Investigation:

Several issues were identified following principal investigator interviews and discussion with animal program staff:

1) For incidences 1 and 2, the intended breeding program was not described in sufficient detail so that it could be clearly followed and would accurately reflect the numbers estimated and produced on the protocols. There was also inadequate communication about rodent breeding instructions from the laboratory staff to the technicians setting up breeding pairs.

2) Principal investigators did not understand how pups are counted, i.e. that they count at day seven post-birth, even if they are not being retained for experimental use. This information is described in the White Oak Consolidated Animal Program (WOCAP0 ACUC Guidelines for Breeding and Genetic Management of Mice and Rats.

3) These overages were not discovered prior to their occurrence because of an unknown flaw in the communication between the animal census database and the web interface that principal investigators use to track animal totals. It was believed that system notifications would occur for both animal purchases and breeding, but in the investigation, it was determined that notifications only occurred associated with animal purchases. All animals bred in the facility were entered into the census database, however, only the animal program had access to it (not principal investigators) and it was not linked to directly update animal protocol usage. Additionally, in one incident, breeding animals were not being added to the correct protocol, so the overage discovery was delayed.

4) Investigators received weekly or monthly breeding reports stating the number of animals born and weaned in their colonies; however, in each of these incidents, the lab staff were not utilizing the production reports and maintaining their own breeding records accurately. They were instead relying on the web interface to notify them if they were approaching their IACUC-approved animal numbers.

Corrective Actions:

1) Each investigator with overages has submitted an amendment to account for the overages, and are either approved or being reviewed by the IACUC.

2) All investigators met with either the IACUC Chairperson, Vice-Chairperson or the facility veterinarian to discuss the overages and the recordkeeping responsibility for their protocol.

3) A sub-committee of the IACUC convened to examine the issues related to these incidences and determined that additional scrutiny of breeding protocols is required.

    a. The committee will send a letter to all investigators with breeding protocols to clarify their responsibility for tracking and managing animal numbers. This letter will include IACUC breeding guidelines and be copied to upper level management.

    b. An IACUC member will meet with each investigator that has breeding as part of the protocol at the semi-annual review or during the semi-annual laboratory walk-through for those investigators bringing animals to their labs. The IACUC member will examine

the breeding records and/or discuss with the lab staff the breeding component of their IACUC-approved study protocol(s) to clarify expectations and better ensure compliance.

4) A short-term procedural change will be implemented to ensure that notifications occur when the number of animals purchased or born reaches 80% of the approved animal allocation. To accomplish this, the contract staff (POS) will monitor animal usage weekly using the animal census database. POS staff will notify the veterinarian and the IACUC Office when breeding protocols have reached 80% of the animal allocation. The IACUC Office will alert the PI that an action is required to avoid overage.

5) The long-term solution includes a new interface between the census database and the web interface, making animal numbers more accessible to principal investigators. Automatic notifications for animal usage on all protocols will be sent to the principal investigator, POS management and Division of Veterinary Services staff when 80% of the approved animal numbers has been reached. Notification would also occur at 100% of total usage so that the protocol work could be halted, or additional animals approved, prior to a 10% breeding overage occurring.

Ward, Joan (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Wednesday, March 14, 2018 1:31 PM
To: (b) (6)
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Incident Report for FDA White Oak Consolidated Animal Program Assurance A4300-01

Thank you for this report, Ms (b) (6) We will send a response soon.

Axel Wolff, M.S., D.V.M.
Deputy Director, OLAW

From: (b) (6) [mailto (b) (6) @fda.hhs.gov]
Sent: Wednesday, March 14, 2018 12:24 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: (b) (6) (FDA/CDER (b) (6) @fda.hhs.gov>; Dennis, John (FDA/CBER) <John.Dennis@fda.hhs.gov>; Marks, Peter (FDA/CBER) <Peter.Marks@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.

Thank you,

(b) (6)
WOC IACUC Administrator
Division of Veterinary Services
(b) (6)