



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:

Office of Laboratory Animal Welfare
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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

January 13, 2020

Re: Animal Welfare Assurance
A3143-01 [OLAW Case Y]

Dr. Camille P. Wicher
Vice President, Corp. Ethics and
Research Subject Protection
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263

Dear Dr. Wicher,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your January 3, 2020 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at Roswell Park Cancer Institute. According to the information provided, OLAW understands that expired anesthetic (Avertin) and analgesic was used in mice. Specifically, four mice were anesthetized for a uterine transfer of blastocysts and there were no complications due to the use of the expired drugs.

The corrective actions consisted of counseling the investigator who indicated that expired drugs will not be used in the future, that the laboratory will closely monitor expiration dates, and that a standard operating procedure was developed to address the monitoring. The Institutional Animal Care and Use Committee (IACUC) further required the investigator to take online retraining, to take surgical hands on retraining, and to evaluate the use of inhalant anesthesia. The veterinarian determined that use of Avertin was justified to reduce respiratory movement, the investigator provided evidence of hundreds of successful surgeries using the drug, and the IACUC approved the ongoing use of this non-pharmaceutical grade compound for this procedure. Avertin will be used within two weeks of expiration, but other surgical procedures must be done using pharmaceutical grade drugs.

OLAW understands that the protocol involved was not PHS-supported, but concurs that the incidents were serious and supports the actions taken by the IACUC. The establishment and application of policies and practices that are consistent with the provisions of the PHS Policy at Roswell Park Cancer Institute are commendable and avoid the perception of a double standard. Thank you for informing OLAW about this matter.

Sincerely,

(b) (6)

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

cc: IACUC Chair



Camille P. Wicher, Ph.D. Esq., RN, MSN.
Vice President Corporate Ethics
Roswell Park Cancer Institute
Elm & Carlton Sts
Buffalo, New York 14263
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A3143-Y
New case
No prelim.

January 3, 2020

Axel Wolff, DVM.
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
Rockledge 1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982

SENT VIA E-MAIL only

RE: Reports of Non-Compliance
1371M and 928M
OPRR Assurance #A-314301.
USDA Regis. #21-R-032

Dear Dr. Wolff,

Please accept the two attached reports as required by 9 CFR 2.31 (c) (3) and (d) (7) Subchapter A of the Animal Welfare Act, as well as PHS Policy IV.F.3.

Corrective action has been instituted. Roswell Park Cancer Institute is committed to protecting the welfare of animals used in research and appreciates the guidance and assistance provided by OLAW in this regard. Should you have any questions, please do not hesitate to contact me at (b) (6)

Thank you in advance for your cooperation in this matter.

Sincerely,

Camille P. Wicher, PhD., Esq., RN, MSN
Vice President
Institute Official
OPRR Assurance #A-314301.
USDA Regis. #21-R-032

Please accept the following final reports in accordance with 9 CFR 2.31 (c) (3) and (d) (7) Subchapter A of the Animal Welfare Act:

ISSUE: Expired medications Protocol # 928M

SUMMARY:

During the November 2019 semi-annual inspection of procedure room (b) (4) IACUC found an anesthetic expired (Avertin expired 11/2018 & 7/2019) and an analgesic expired (Buprenorphine expired 2018). A memo was sent to the principal investigator, Dr. Y on November 8th noting the expired Avertin and Buprenorphine in procedure room M481 and requesting information about the analgesics used during the mouse surgery on October 25th (928M). Dr. Y responded to the memo on November 14th stating the expired Avertin prepared in July 2019 had been used for the surgery on October 25th. The memo also stated that the expired Buprenorphine had been used as the analgesic. The memo also stated that in the future only Avertin within 2 weeks of preparation will be used and expired Buprenorphine will not be used. Dr. Y admitted the mistake.

The IACUC responded to Dr. Y's memo on November 15th requesting additional information and clarification regarding the surgical procedure in which expired Avertin was used as the anesthetic and expired Buprenorphine was given as the analgesic during the recovery period on the mice on October 25, 2019. The additional information requested:

- The description of the surgical procedure that was performed October 25, 2019.
- Number of mice that underwent the surgical procedure.
- Individuals that were involved in the surgical procedure (surgeon, assistant, etc.).
- Any complications that may have been observed with any of the mice during or after the surgical procedure.
- Confirm if this is a PHS funded experiment.
- Any additional information you deem relevant to the investigation.

Dr. Y responded promptly to the memo on November 16th and provided the requested information.

The surgical procedure was uterine transfer of blastocysts. The uterine transfer procedure had been performed on 4 mice and Dr. Y was the only individual involved with the surgeries. No complications were observed with any of the mice during or after the surgical procedure. The research was not funded by the PHS but by a private foundation. In addition, Dr. Y stated he did not realize the anesthetic compounds and drugs were expired and he regrets the oversight. He indicated that use of expired medications will not happen again. Included with the response was a Standard Operating Procedure (SOP) that describes the newly instituted methods in Dr. Y's laboratory for close monitoring of anesthetics (i.e., Avertin) and analgesics (i.e., buprenorphine and Marcaine) so that expired aforementioned drugs will not be used in the future. The SOP states these drugs (Avertin, Buprenorphine, and Marcaine) will be monitored closely, and information documented.

The use by Dr. Y (protocol 928M) of expired avertin and Buprenorphine on four mice that underwent uterine transfer of blastocysts 10/25/2019) was discussed by the IACUC committee at their December 2019 monthly meeting (12/03/2019). The IACUC determined that this was an animal welfare issue and a reportable event. The IACUC reviewed Dr. Y's Corrective and Preventative Plans of Action (CAPA) and approved the increased monitoring and documentation of anesthetics and analgesics. However the IACUC requested additional actions prior to approval for the continued use of Avertin for uterine transfer procedures on any mice enrolled in protocol 928M. The additional actions requested by the IACUC are listed below and were sent to Dr. Y on December 4, 2019:

- Dr. Y complete the AALAS online mouse surgical module and quiz. **(completed 12/08/2019)**
- Dr. Y complete LASR's Surgical Wet Lab training. **(completed 12/12/2019)**
- Dr. Y contact LASR Veterinary Services and discuss the use of isoflurane and the availability of smaller nose cones etc. for the administration of isoflurane. **(completed 12/12/2019)**
- Dr. Y demonstrate the uterine transfer procedure (as a terminal procedure) using Avertin as the anesthetic and then perform another uterine transfer procedure on a second mouse using isoflurane as the anesthetic. A LASR veterinarian will provide an assessment to the IACUC as to whether Dr. Y can switch to the use of isoflurane for the uterine transfer procedure or needs to continue to use Avertin. **(completed 12/12/2019)**
- Dr. Y provide any historical information regarding his experience using Avertin (i.e. number of years, how many mice (estimate 10's, 100s, etc.), any complications that he remembers and if so the cause (if known). This historical use of Avertin by Dr. Y will also be reviewed by the subcommittee prior to their determination if Dr. Y can continue to use Avertin. **(Received 12/13/2019)**

The IACUC established a subcommittee of four members including the Chair to review the veterinarian's assessment of both procedures and use this assessment along with any historical data to assist with the IACUC determination regarding whether or not Dr. Y can successfully use isoflurane for the uterine transfer procedure or needs to continue to use Avertin a non-pharmaceutical compound.

The IACUC received the assessment of Dr. Y and the use of Avertin and isoflurane for uterine transfer of blastocysts from the Attending Veterinarian Dr. Sexton on December 13, 2019.

Dr. Sexton reported: Dr. Y is aware of the refinements when using isoflurane and was open to trying the nose cone using the techniques and he demonstrated the ability to successfully use isoflurane. A big concern of Dr. Y was the excessive movement at respiration when the animals were anesthetized with isoflurane. Dr. Y was set up in the bio bubble room a demonstrated the difference in respiration when using Avertin. Dr. Sexton reported that the mouse anesthetized with isoflurane had a higher respiration rate and subsequently more body movement than the mouse anesthetized with Avertin. Dr. Sexton agreed with Dr. Y that for the uterine transfer of blastocysts using glass pulled micropipettes Avertin was a better anesthesia due to the greater reduction in respiration and therefore less movement than when using isoflurane.

Roswell Park Cancer Institute
January 03, 2020

The IACUC Chair sent Dr. Sexton's assessment as well as historical information provided by Dr. Y stating that he had performed over 550 uterine transfers and had never observed any complications associated with the use of Avertin to the sub-committee (e-mail 12/13/2019). The sub-committee approved the continued use of Avertin, a non-pharmaceutical grade compound as the anesthetic for the uterine transfer procedure, as per the original protocol. All surgical procedures (928M) other than uterine transfer require the use of pharmaceutical grade anesthetics (as currently approved in 928M).

The IACUC sub committee believes that Dr. Y's amended CAPA addresses sufficiently the root causes, the corrective plans needed and the preventative processes to prevent a recurrence of this non-compliance. The IACUC believes this an animal welfare concern and therefore may be reportable. It should be noted that Dr. Y was very responsive to the committee's requests and was open to IACUC's suggestions.

As IO I concur with the IACUC's findings and corrective actions.

Respectfully submitted,

(b) (6)

Camille P. Wicher, Ph. D. Esq. RN MSN
Institutional Official
Vice President
Roswell Park Cancer Institute

Morse, Brent (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Monday, January 06, 2020 7:38 AM
To: Wicher, Camille; OLAW Division of Compliance Oversight (NIH/OD)
Cc: (b) (6) Moser, Michael
Subject: RE: Reports of non-compliance

Thank you for this report Dr. Wicher. 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

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From: Wicher, Camille [mailto:Camille.Wicher@RoswellPark.org]
Sent: Friday, January 03, 2020 1:44 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: (b) (6) Moser, Michael <Michael.Moser@RoswellPark.org>
Subject: Reports of non-compliance

Dr. Wolff, Attached please find two reports. One is for non-compliance (1371M) and the other for use of expired medications (928M). If you have any questions please do not hesitate to contact me. Happy New Year! Camille

Camille P. Wicher, Ph.D., Esq. MSN, RN
Assistant Professor of Oncology
Vice President
Roswell Park
Elm & Carlton Sts.
Buffalo, New York 14263

(b) (6)

