



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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Home Page: <http://grants.nih.gov/grants/olaw/olaw.htm>

FOR EXPRESS MAIL:

Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 402-7065

August 15, 2017

Re: Animal Welfare Assurance
#A4261-01 (OLAW Case N)

Mr. Steven M. Glaza
Vice President and Institutional Official
SNBL USA, Ltd.
6605 Merrill Creek Parkway
Everett, WA 98203

Dear Mr. Glaza,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your August 8, 2017 email containing the report of an adverse event within your animal care and use program that occurred on July 26, 2017. According to the information provided, OLAW understands that a rhesus macaque died during a scheduled apheresis procedure. This is the first animal death during the apheresis procedure conducted at SNBL. There have been 15 separate procedures conducted since 2014. This animal was supported by PHS (BARDA) funds.

After reviewing all documents pertaining to the death of the animal during the apheresis procedure, no definitive cause of death was determined. These documents included the animal's medical record; blood collection and processing of donor blood for priming of the apheresis machine; anesthesia initiation and monitoring sheets; ancillary form for all supplies used, and; all training records of personnel involved in the procedure.

Possible factors that may have contributed to the death of the animal are: the prolonged delay in the apheresis procedure; the loss of catheter patency; inherent risk of the procedure; risk of a long anesthetic period; immune response to donor blood, and; idiopathic condition in the animal.

Corrective actions included: having the apheresis machine vendor service the machine; training appropriate personnel on performing general anesthesia and emergency procedures with an emphasis on apheresis; developing a more robust preoperative physical exam, and; monitoring calcium both during and post apheresis.

The prompt consideration of this matter by SNBL USA was consistent with the philosophy of institutional self-monitoring, self-reporting and self-correction. Similarly, the actions taken to resolve the issue and prevent recurrence were appropriate. OLAW makes one observation that your institution may have already considered: although the veterinarian should be allowed to use clinical judgement during such procedures, it may benefit the institution and the animals if SOP's and/or protocols used to guide such procedures have specific endpoints reviewed and approved by the IACUC and the veterinarian that would call for a procedure to be stopped completely if certain time points are not met or certain difficulties are encountered.

We appreciate being informed of this matter and find no cause for further action by this office at this time.

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Sincerely,

A handwritten signature in black ink, appearing to read "Brent Morse", with a long horizontal flourish extending to the right.

Brent C. Morse, DVM
Acting Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare

cc: IACUC Contact

Dr. Robert M. Gibbens, Director Western Sector, USDA, APHIS, AC

Investigation Report:Re: SNBL. [REDACTED], SSAN 1001, 142727:

Animal SSAN 1001, 142727, was anesthetized on 07/26/17 for a scheduled apheresis procedure in support of study SNBL. [REDACTED].

Personnel:

Surgeon: [REDACTED], DVM, DACLAM [REDACTED] dary ind

Apheresis: [REDACTED], Surgical Specialist/Trainer [REDACTED] ndary indivi

Anesthesia: [REDACTED], Research Associate I [REDACTED] ndary indiv

Necropsy: [REDACTED] and [REDACTED] ndary indivi

Timeline:

- 08:30 AM: Peripheral indwelling catheters were placed in the left cephalic and saphenous veins by [REDACTED] and [REDACTED] dary indi
- 08:35 AM: The animal was placed on the surgical table, the gas anesthesia and the anesthetic monitoring was initiated [REDACTED] dary ind
- 08:45 AM: Surgical exposure of the right femoral vein was performed by [REDACTED] dary in After the surgical exposure of the femoral vein, the surgeon experienced difficulty in advancing the catheter into the vein. The catheter was eventually advanced and the apheresis procedure was started but the catheter was partially occluded causing the machine to sense over-pressure and automatically pause the procedure. The catheter was removed and replaced to correct the occlusion. However, due to the clotted blood in the apheresis lines, the kit was replaced with a new apheresis kit and new donor blood. During the re-priming of the apheresis machine, error codes were observed; all codes were identified and corrected.
- 10:49 AM: The apheresis procedure was initiated with a new apheresis kit and donor blood. Saline/calcium gluconate maintenance began using the catheter in the left cephalic vein. During the early phase of the procedure, the machine inlet/return pressure recording was reading high at the flow rate set at 30ml/min. The flow rate was decreased from 30 ml/min to ~23ml/min and no further observations related to the inlet/return pressure were noted. The first cycle was then completed.
- 11:48 AM: Routine anesthetic monitoring and adjustments performed according to the values observed by [REDACTED] dary in the animal had a decrease in HR from 149 to 139 bpm and the gas anesthesia % was decreased from 2.5 to 2.0 % (appropriate action) by [REDACTED] dary in respiration rate at 20 per minute, mm=pink, CRT 1-3 sec., CO2 (mmHg) 59.
- 12:15 PM: Percent gas concentration was further decreased to 1.5%, HR 118 bpm, RR 9 per min., mm=pale, CRT 1-3 sec. and CO2 mmHg 67 [REDACTED] dary ind
- 12:15 PM: The left forearm was observed to be swollen. This was consistent with the animal having lost catheter patency on the left cephalic vein for the saline/calcium gluconate drip [REDACTED]

- 12:15 PM: A call was made to the veterinarian that the animal had an increase in CO2 mmHg.
- 12:18 PM: The animal was in cardiac and respiratory arrest and emergency CPR was initiated, epinephrine, atropine and Doxapram IV were administered dary inc
- 12:27 PM: Time of death.
- 1:19 PM: Gross necropsy was performed and was unremarkable for the major organs collected.

All anesthetic animal monitoring parameters were within acceptable range while under anesthesia for approximately four hours before the animal experienced complications following the first apheresis cycle. The animal's condition deteriorated rapidly and the animal expired despite administering emergency CPR.

Documents reviewed:

- The entire SNBL animal medical record for animal 142727
 - Animal was within the acceptable parameters for the study.
- Blood collection and processing (including filtering and irradiating) of donor blood for priming of the apheresis machine.
 - All steps were followed as described in the SOP. No discrepancies observed. The protocol for blood collection is the standard used on other studies requiring use of donor blood. No history of donor/recipient reaction has occurred using this protocol.
- Anesthesia initiation and anesthesia monitoring sheets.
 - Changes in the animal parameters and adjustments of gas anesthetic percent concentration were documented. The changes initiated were appropriate actions to the changes in animal's anesthetic depth.
- Ancillary form for all supplies used.
 - All solutions, anticoagulants, medications used were within the expiration dates.
- All training records of personnel involved in the procedure.
 - All personnel were proficient for their respective tasks and all pertinent documents were in order.

After reviewing all documents pertaining to the death of the animal during the apheresis procedure, no definitive cause of the death was determined. Possible factors that may have contributed to the death of the animal are the following:

- 1) The prolonged delay of the apheresis procedure (i.e. surgical placement of the catheter, correction of error codes from the apheresis unit, and re-priming of the apheresis unit).
- 2) The loss of catheter patency of the left cephalic vein for the IV infusion of saline/calcium gluconate supplement solution.
- 3) The inherent risk associated with the apheresis procedure.

- 4) The risk associated with procedures requiring long anesthetic periods.
- 5) Immune response to donor blood
- 6) Idiopathic condition in the animal

Corrective actions:

- The Fenwal vendor was contacted and performed service on machine on 08/03/17 to address the code errors encountered during the apheresis and to perform any additional service on the machine to ensure the machine is in proper working condition.
- All personnel scheduled on performing general anesthesia and monitoring of animals will undergo additional training on theory and concept of general anesthesia and emergency procedures with an emphasis of apheresis procedures. The training will be accomplished prior to the next scheduled apheresis procedure.
- A more robust preoperative physical exam will be developed that may include a clinical pathology assessment and a comprehensive cardiac exam.
- Calcium monitoring (at least every 2 hours) both during and post apheresis procedures will be included in patient monitoring.

Wolff, Axel (NIH/OD) [E]

From: Wolff, Axel (NIH/OD) [E]
Sent: Wednesday, August 09, 2017 7:15 AM
To: 'Steve Glaza'
Subject: RE: Notification of Animal Death

Thank you for this report, Mr. Glaza. We will send a response soon.
Axel Wolff

From: Steve Glaza [mailto:SGlaza@SNBLUSA.com]
Sent: Tuesday, August 08, 2017 3:10 PM
To: Wolff, Axel (NIH/OD) [E] <WolffA@OD.NIH.GOV>
Cc: Secondary Individual @SNBLUSA.com>; Secondary Individual @SNBLUSA.com>; Secondary Individual @SNBLUSA.com>; Secondary Individual @SNBLUSA.com>; Secondary Individual @SNBLUSA.com>; Secondary Individual @SNBLUSA.com>; Steve Glaza <SGlaza@SNBLUSA.com>; Secondary Individual @SNBLUSA.com>; Secondary Individual @SNBLUSA.com>; Secondary Individual @SNBLUSA.com>; Secondary Individual @SNBLUSA.com>;
Subject: Notification of Animal Death

Dear Dr. Wolff,

This is to notify your office that it has been recently reported that on July 26, 2017 a rhesus macaque died during the course of a blood apheresis procedure within a PHS (BARDA) funded study (SNBL 684.04) being conducted at our Everett, WA facility. The details of this animal death and the resulting detailed investigation and corrective actions are outlined in the attached document. It should be noted that this is the first animal death that we have experienced during the apheresis procedures conducted at our facility (15 separate procedures conducted since 2014).

Please let me know if there are any questions about this matter.

Best regards,

Steve Glaza
Vice President-SRC and Institutional Official
SNBL USA, Ltd.

T. Phone Number (WA office)

T. Phone Number (TX office)