DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive - MSC 7982
Bethesda, Maryland 20892-7982
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

June 23, 2017

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

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 a copy of your May 31, 2017 letter to Dr. Diane Forbes, VMO, USDA responding to findings noted in the May 5, 2017 inspection of the Everett facility of SNBL USA. Your letter supplements information supplied to OLAW by USDA, APHIS, Animal Care. According to the information provided, OLAW understands that there were three findings by USDA:

Finding No. 1 – This involved full-thickness loss of skin in 40 Guinea Pigs on a skin irradiation study. Fifty-six animals were subjected to the irradiation and of the 40 animals with lesions, 14 were noted as exhibiting distress and were evaluated by the Veterinary Services group. Ten animals had been given analgesic treatment and other directed interventions. This study was classified by the IACUC as USDA Pain Category "D" *Pain or distress relieved by analgesia or anesthesia* although not all irradiated animals had been treated with analgesia or anesthesia or other interventions.

Corrective actions included a greater emphasis in preparing pre-emptive treatment plans for all irradiation and preclinical toxicology studies. SNBL's Humane Endpoints Policy will be updated to categorize these types of dermal lesions as Category D. Applicable personnel will be retrained on these changes.

Finding No. 2 – This involved a general finding related to findings No.1 and No.2 regarding prompt notification to the Attending Veterinarian of potential animal health concerns.

Corrective actions included assigning each protocol to a primary veterinarian and additional communications and retraining of all applicable vivarium staff.

Finding No. 3 – This involved a cynomolgus macaque that was restrained for a study protocol on February 6, 2017. All animal handling was conducted using a procedure box, to which it had been acclimatized. Within a few hours it had been observed at least twice that there were abnormalities with the animal's left forelimb regarding appearance and/or function but it was not until approximately 20 hours after the initial abnormal observation that the veterinary staff were notified. The animal was subsequently euthanized.

Corrective actions included disciplinary action with the personnel involved. Also, the applicable SOP associated with neurological assessments in primates is under revision to improve the directive to immediately report any findings that are potentially impacting an animal's health and to request a veterinary assessment. All applicable staff will be retrained and certified in the updated requirements.

It was noted that one of the Guinea Pig activities was funded by BARDA

The prompt consideration of these matters by SNBL USA was consistent with the philosophy of institutional self-correction. Similarly, the actions taken to resolve the issues and prevent recurrences were appropriate. Although not all activities were PHS funded, the application of the standards of the PHS Policy across the animal care and use program reduces any potential appearance of a double standard. OLAW requests that in the future you provide this office with a prompt preliminary report if a USDA citation involves, or has the potential to involve, animals funded by the PHS or NSF. We are available to discuss specifics regarding appropriate reporting to OLAW.

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

Sincerely,

Brent C. Morse, DVM
Animal Welfare Program Specialist
Division of Compliance Oversight
Office of Laboratory Animal Welfare

cc: IACUC Contact
Dr. Robert M. Gibbens, Director Western Sector, USDA, APHIS, AC

SNBL USA
PRECLINICAL SERVICES FOR DRUG DEVELOPMENT

SNBL USA, Ltd. • 6605 Merrill Creek Parkway • Everett, WA 98203 • Tel: 425 407 0121 • Fax: 425 407 8601

May 31, 2017

Diane Forbes, DVM
Veterinary Medical Officer
USDA - APHIS
Animal Care, Western Region
2150 Centre Ave., Building B
Mail Stop # 3W11
Fort Collins, CO 80526-8117

Re: Follow up to USDA Inspection for Registration 91-R-0053 and Class B License 91-B-0078

Dear Dr. Forbes,

SNBL USA would like to take this opportunity to follow up with you regarding the findings noted in the May 5, 2017 inspection of our Everett facility conducted by you and Dr. Michael Schnell. As you know, there were no non-compliant items identified during the inspection with respect to the 91-B-0078 license.

We sincerely appreciated USDA's acknowledgement of SNBL's hard work and the resulting pattern of continuous improvement in our overall animal welfare program, including the realignment of our Husbandry, Veterinary Services and Facilities under one cohesive management structure and the continued improvement shown in our animal behavioral observations and tracking. We appreciate the insights you and Dr. Schnell provided during the course of the inspection and, based on these comments, as well as our own internal assessment, have taken the following steps to address the three findings associated with the 91-R-0053 license:

Finding No. 1

2.31(e)(4) DIRECT
INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC).

A protocol approved by the Institutional Animal Care and Use Committee (IACUC) involving full-thickness skin irradiation in guinea pigs categorized 28 males and 28 females as "Pain or distress relieved by analgesia or anesthesia."

The protocol also later states that "Pain, distress and/or irritation are not an expected outcome; however, if deemed necessary by veterinary assessment, non-NSAID analgesics (e.g. buprenorphine...) and diphenhydramine may be provided, as needed. This latter statement is contradictory to the classification as "Pain or distress relieved by analgesia or anesthesia."

At the time of the inspection, forty (40) animals had open wounds (partial to full-thickness loss of skin at the irradiated site) and varying degrees of redness and swelling immediately surrounding the irradiated site indicating substantial inflammation. The test facility noted 19 animals with "distress when picked up from cage and has an open wound at the irradiation site." These signs could be interpreted as evidence of "pain, distress and/or irritation" noted within the protocol as a basis for provision of analgesia. A total of 10 animals were treated with buprenorphine by the test facility based upon general clinical signs and a supportive provision of a food cup in place of a feeder to make it easier for them to eat.

The protocol classification approved by the IACUC as Category D "Pain or distress relieved by analgesia or anesthesia" requires administration of analgesia or anesthetics. By not providing analgesia or anesthesia in these affected animals renders them as Category E "Unrelieved pain or distress."

A protocol approved by the IACUC must contain a clear description of the procedures designed to assure that discomfort and pain to animals will be limited to that which is unavoidable for the conduct of scientifically valuable research, including provision for the use of analgesic, anesthetic, and tranquilizing drugs where indicated and appropriate to minimize discomfort and pain to animals. A scientific justification is required for animals that experience unrelieved pain or distress and such justification must be approved by the IACUC.

Unless such approved justification exists, an animal that can be reasonably be expected to experience more than slight or momentary pain and/or distress like these animals must receive analgesics, anesthetics and/or or other interventions appropriate to the nature and severity of the pain, discomfort or distress. Such methods of relief must be approved by the IACUC.

SNBL Response to Finding No. 1

Upon review of the study data associated with this issue, we would first like to point out that only 14 animals were noted as exhibiting "distress when picked up from cage," rather than 19 as the observation states. These specific animal observations made by SNBL staff were reported that same day to our Veterinary Services group, who immediately evaluated the animals, observed that the animals did not appear to be in any pain or distress, and therefore prescribed additional monitoring. As noted in the USDA inspection report, SNBL had already initiated analgesic treatment and other directed interventions for ten of the animals on this study at the time of the USDA inspection. SNBL additionally followed an analgesic treatment plan throughout the remainder of the study for all animals that had severe/full thickness dermal lesions and/or were exhibiting distress or pain.

Corrective Actions: SNBL has undertaken the following corrective actions related to the findings described above:

- There will be greater emphasis placed in preparing pre-emptive veterinary treatment plans for all irradiation and preclinical toxicology studies conducted at SNBL USA, with special provisions for implementing analgesic treatments to alleviate any anticipated pain or distress the animals may encounter. SNBL has implemented this enhanced emphasis process for all current and future studies as a shared responsibility between the assigned Study Director (PI), Veterinary Services and the SNBL IACUC.

- To ensure that full-thickness dermal lesions are deemed to be painful and are properly treated accordingly, we will update the SNBL Humane Endpoints Policy (IAC.008) to categorize these types of dermal lesions as Category D and thus requiring analgesics to relieve any pain or distress. This formal policy revision will be implemented by June 16, 2017.

- SNBL will complete by June 30, 2017 retraining of all applicable study directors, vivarium staff (including Veterinary Services) and IACUC members on the need for and adherence to these pre-emptive veterinary treatment plans and the assessment/treatment of dermal lesions.

Finding No. 2

2.33(e)(5) CRITICAL REPEAT
ATTENDING VETERINARIAN AND ADEQUATE VETERINARY CARE.

In a protocol involving non-human primates, one of the monkeys sustained a fracture of the two long bones of the left forearm. Although lack of use and favoring of the affected limb was noted by facility personnel on two separate occasions on two days, the veterinarian was not contacted until approximately 19-20 hours after the first such observation. This monkey was subsequently euthanized shortly after veterinary examination. Fractures cause pain, which can be quite severe depending upon the location and severity of the fracture. While the fracture was unanticipated, the lack of reporting caused this animal to experience pain longer than had it been reported to the veterinary staff when initially noticed.

In a protocol involving full-thickness irradiation of guinea pigs, the approved protocol stated that pain or distress was not anticipated (despite categorization of the majority of animals as Category D) but pain relief would be provided if deemed necessary upon veterinary assessment. Forty (40) animals experienced outcomes (partial to full-thickness skin loss of skin caused by the irradiation) that could reasonably be expected to cause more than slight or momentary pain and/or distress. Of these, ten (10) animals were treated with buprenorphine.

In the event that unexpected pain or distress would occur in an animal, the attending veterinarian must be promptly contacted to assure expedient and appropriate action is taken to alleviate the pain, distress or discomfort. The affected animal must receive analgesics, anesthetics or other interventions appropriate to the nature and severity of the pain, discomfort or distress.

SNBL Response to Finding No. 2
The current SNBL SOP-driven processes for the evaluation of animal health conditions and the timely reporting of these conditions to the staff veterinarians for their subsequent follow-up and treatment are well established. However, additional communications and the retraining of all applicable vivarium staff that the reporting of any potential animal health concern must be made promptly to the Veterinary Services staff at SNBL in order to provide the most expedient evaluation and treatment of these animals will be completed by June 19, 2017.

Additionally, a realignment of veterinarian responsibilities is occurring in that each protocol is assigned to a primary veterinarian for oversight, review and on-going monitoring during day-to-day operations.

Finding No. 3

2.38(f)(1) CRITICAL REPEAT
MISCELLANEOUS.

On 06 February 2017, a cynomolgus macaque on a study protocol received fractures of the radius and ulna. On that morning, the monkey received a baseline neurological/musculoskeletal evaluation with no abnormalities detected. Blood was then collected minutes later for two separate evaluations. Approximately two-and-a-half hours later, the monkey was restrained for administration of a test article. All animal handling was conducted using a procedure box, to which it had been previously acclimatized.

Observation of the animal on a scheduled neurological/musculoskeletal evaluation conducted approximately four hours post-dose indicated that it could grasp with the left hand when the squeeze back was used, but not using that hand when left alone. Clinical observations approximately one hour later indicated bruising of the right lower forelimb and right hind limb, as well as a scab/crust of an upper hind limb.

Scheduled clinical observations and neurological/musculoskeletal evaluation the next morning were consistent with those on the previous day. An unscheduled clinical observation was performed approximately 20 hours after the first abnormal neurological/musculoskeletal evaluation. This observation included consistent results as previous observations but included swelling of the lower left forelimb.

A veterinary examination was conducted within minutes of this latter observation, which indicated no use of the left arm, mild swelling to the forearm, with a planned sedation for x-ray and limb palpation. This latter evaluation revealed displaced fractures of the radius and ulna. The monkey was then euthanized. The veterinary assessment was conducted approximately 20 hours after the initial abnormal observation due to lack of reporting to the veterinary staff.

While the exact cause of the fractures was not determined by the test facility, the "Animal Welfare Incident Report" submitted to the facility Institutional Animal Care and Use Committee stated that "the injury most likely occurred during the Feb. 6th blood collection and/or dosing."

The test facility must assure that the handling of all animals is conducted as expeditiously and carefully as possible in a manner that does not cause trauma, overheating, excessive cooling, behavioral stress, physical harm, or unnecessary discomfort.

During this inspection, it was noted that the test facility has enacted a number of improvements with regards to the welfare, training and behavior and environmental enhancements since the last inspection. These changes include a re-organization to align husbandry, study and veterinary staff under one cohesive line of management and improved observation and tracking of behavioral conditions.

SNBL Response to Finding No. 3

We take great time and effort to train our technical staff in the proper care and restraint of all animals, particularly primates, and use innovative techniques and positive reinforcement with the animals to minimize any handling difficulties. The data record for this affected animal does indicate that it had favoring of the left hand during neurological assessment on the afternoon February 6, 2017 although the technician making the observation at that time did not feel that the finding was associated with a possible arm fracture. It was during the observations made the next morning on February 7, 2017 that the favoring of the hand/arm was more pronounced and as a result the subsequent veterinary assessment confirmed the fracture. Veterinary treatment and remediation then followed.

Corrective Actions:

- The applicable SOP (EVR.SOP.HEA.028) associated with neurological assessments in primates is currently under revision to improve the directive to immediately report any findings that are potentially impacting an animal's health and to request a veterinary assessment. This SOP revision will be completed by June 16, 2017. All applicable staff will be retrained and recertified in these updated requirements by June 16, 2017.

- Additionally, disciplinary action has been taken with the personnel involved in the reporting of the findings associated with this animal's injury.

SNBL USA continues to take our responsibilities regarding animal welfare very seriously and we remain committed to ensuring the proper care and use of animals within our facilities. We also appreciate the USDA's collaborative approach and willingness to contribute to this commitment as well. Should you have any questions regarding this follow up report, please do not hesitate to contact me [redacted] or at sglaza@snblusa.com)

Sincerely,

Steven M. Glaza
Vice President and Institutional Official
SNBL USA, Ltd.

Cc: IACUC Administrator

Wolff, Axel (NIH/OD) [E]

From: Wolff, Axel (NIH/OD) [E]
Sent: Thursday, June 01, 2017 7:43 AM
To: 'Steve Glaza'
Subject: RE: Notification of Recent USDA Inspections of SNBL USA

Thank you for these reports, Mr. Glaza. We will send you an official response shortly.

Axel Wolff

From: Steve Glaza [mailto:SGlaza@SNBLUSA.com]
Sent: Wednesday, May 31, 2017 6:53 PM
To: Wolff, Axel (NIH/OD) [E] <WolffA@OD.NIH.GOV>
Cc: Secondary Individual @SNBLUSA.com>; Secondary Individual @SNBLUSA.com>; Secondary Individual ndary Indiv @SNBLUSA.com>; Steve Glaza <SGlaza@SNBLUSA.com>
Subject: Notification of Recent USDA Inspections of SNBL USA

Hello Dr. Wolff,

This is to inform the OLAW office that the USDA APHIS Division has conducted two recent inspections of our Everett facility. These inspections are summarized below:

- A focused USDA inspection was conducted on May 1, 2017 covering both our research registration and Class B license (inspection reports issued on May 5, 2017). The inspection reports are attached for your reference. Please note that there were no citations related to the Class B license.
- Today, May 31st, SNBL has issued its formal response letter to the USDA regarding May 5th inspection report (see attached). Please note that the one guinea pig study noted in the first citation is a BARDA funded project.
- On May 30th, the two USDA inspectors who conducted the May 1st inspection performed a follow-up inspection at our Everett facility and concentrated on the remediation steps that SNBL had previously committed to in regards to this guinea pig study. They found that everything was in order and they issued the attached inspection report with no citations noted.

If you should have any questions regarding these matters please feel free to contact me.

With best regards,

Steve

Steve Glaza
Vice President-SRC and Institutional Official
SNBL USA, Ltd.
T. Phone Number (WA office)
T. Phone Number (TX office)

A 4261-M DFORBES

USDA

United States Department of Agriculture
Animal and Plant Health Inspection Service

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Inspection Report

Snbl Usa Ltd
6605 Merrill Creek Parkway
Everett, WA 98203

Customer ID: **11124**
Certificate: **91-R-0053**
Site: 001
SNBL USA, LTD

Type: FOCUSED INSPECTION
Date: 01-MAY-2017

2.31(e)(4) DIRECT

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC).

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At the time of the inspection, forty (40) animals had open wounds (partial to full-thickness loss of skin at the irradiated site) and varying degrees of redness and swelling immediately surrounding the irradiated site indicating substantial inflammation. The test facility noted 19 animals with "distress when picked up from cage and has an open wound at the irradiation site." These signs could be interpreted as evidence of "pain, distress and/or irritation" noted within the protocol as a basis for provision of analgesia. A total of 10 animals were treated with buprenorphine by the test facility based upon general clinical signs and a supportive provision of a food cup in place of a feeder to make it easier for them to eat.

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Prepared By: DIANE FORBES Digitally signed by DIANE FORBES DN: c=US, o=U.S. Government, ou=Department of Agriculture, cn=DIANE FORBES, 0.9.2342.19200300.100.1.1=12001000107285 Date: 2017.05.05 07:37:03 -07'00'

FORBES DIANE, D V M USDA, APHIS, Animal Care

Title: VETERINARY MEDICAL OFFICER 5053

Date: 05-MAY-2017

Received By:

STEVE GLAZA VIA EMAIL

Title: INSTITUTIONAL OFFICIAL

Date: 05-MAY-2017

experience unrelieved pain or distress and such justification must be approved by the IACUC.

Unless such approved justification exists, an animal that can be reasonably be expected to experience more than slight or momentary pain and/or distress like these animals must receive analgesics, anesthetics and/or or other interventions appropriate to the nature and severity of the pain, discomfort or distress. Such methods of relief must be approved by the IACUC.

Correct from this time forward.

2.33(e)(5) CRITICAL REPEAT

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2.38(f)(1) CRITICAL REPEAT

MISCELLANEOUS.

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FORBES DIANE, D V M USDA, APHIS, Animal Care

Title: VETERINARY MEDICAL OFFICER 5053

Date: 05-MAY-2017

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Date: 05-MAY-2017

Inspection Report

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On that morning, the monkey received a baseline neurological/musculoskeletal evaluation with no abnormalities detected. Blood was then collected minutes later for two separate evaluations. Approximately two-and-a-half hours later, the monkey was restrained for administration of a test article. All animal handling was conducted using a procedure box, to which it had been previously acclimatized.

Observation of the animal on a scheduled neurological/musculoskeletal evaluation conducted approximately four hours post-dose indicated that it could grasp with the left hand when the squeeze back was used, but not using that hand when left alone. Clinical observations approximately one hour later indicated bruising of the right lower forelimb and right hind limb, as well as a scab/crust of an upper hind limb.

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A veterinary examination was conducted within minutes of this latter observation, which indicated no use of the left arm, mild swelling to the forearm, with a planned sedation for x-ray and limb palpation. This latter evaluation revealed displaced fractures of the radius and ulna. The monkey was then euthanized. The veterinary assessment was conducted approximately 20 hours after the initial abnormal observation due to lack of reporting to the veterinary staff.

While the exact cause of the fractures was not determined by the test facility, the "Animal Welfare Incident Report" submitted to the facility Institutional Animal Care and Use Committee stated that "the injury most likely occurred during the Feb. 6th blood collection and/or dosing."

The test facility must assure that the handling of all animals is conducted as expeditiously and carefully as possible in a manner that does not cause trauma, overheating, excessive cooling, behavioral stress, physical harm, or unnecessary discomfort.

During this inspection, it was noted that the test facility has enacted a number of improvements with regards to the welfare, training and behavior and environmental enhancements since the last inspection. These changes include a re-organization to align husbandry, study and veterinary staff under one cohesive line of management and improved

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FORBES DIANE, D V M USDA, APHIS, Animal Care

Date: 05-MAY-2017

Title: VETERINARY MEDICAL OFFICER 5053

Received By:

STEVE GLAZA VIA EMAIL

Date: 05-MAY-2017

Title: INSTITUTIONAL OFFICIAL

observation and tracking of behavioral conditions.

This inspection and exit briefing were conducted with facility representatives.

Additional Inspectors

Schnell Michael, Veterinary Medical Officer

Prepared By: DIANE FORBES Digitally signed by DIANE FORBES DN: c=US, o=U.S. Government, ou=Department of Agriculture, cn=DIANE FORBES, 0.9.2342.19200300.100.1.1=12001000107285 Date: 2017.05.05 07:39:14 -07'00'

FORBES DIANE, D V M USDA, APHIS, Animal Care

Date: 05-MAY-2017

Title: VETERINARY MEDICAL OFFICER 5053

Received By:

STEVE GLAZA VIA EMAIL

Date: 05-MAY-2017

Title: INSTITUTIONAL OFFICIAL

USDA

United States Department of Agriculture
Animal and Plant Health Inspection Service

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Inspection Report

Snbl Usa Ltd
6605 Merrill Creek Parkway
Everett, WA 98203

Customer ID: **11124**
Certificate: **91-R-0053**
Site: 001
SNBL USA, LTD

Type: FOCUSED INSPECTION
Date: 30-MAY-2017

No non-compliant items identified during this inspection.

This inspection and exit briefing were conducted with the facility representatives.

Additional Inspectors

Schnell Michael, Veterinary Medical Officer

Prepared By: DIANE FORBES Digitally signed by DIANE FORBES DN: c=US, o=U.S. Government, ou=Department of Agriculture, cn=DIANE FORBES, 0.9.2342.19200300.100.1.1=12001000107285 Date: 2017.05.30 17:15:55 -07'00'

FORBES DIANE, D V M USDA, APHIS, Animal Care

Title: VETERINARY MEDICAL OFFICER 5053

Date: 30-MAY-2017

Received By:

STEVE GLAZA VIA EMAIL

Title: INSTITUTIONAL OFFICIAL

Date: 30-MAY-2017

United States Department of Agriculture
Animal and Plant Health Inspection Service

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Inspection Report

Snbl Usa Ltd
6605 Merrill Creek Parkway
Everett, WA 98203

Customer ID: **11124**
Certificate: **91-B-0078**
Site: 001
SNBL USA LTD

Type: FOCUSED INSPECTION
Date: 01-MAY-2017

No non-compliant items identified during this inspection.

This inspection and exit briefing were conducted with facility representatives.

Additional Inspectors

Schnell Michael, Veterinary Medical Officer

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Date: 2017.05.05 07:40:38 -07'00'

FORBES DIANE, D V M USDA, APHIS, Animal Care

Date: 05-MAY-2017

Title: VETERINARY MEDICAL OFFICER 5053

Received By:

STEVE GLAZA VIA EMAIL

Title: VICE PRESIDENT

Date: 05-MAY-2017

Morse, Brent (NIH/OD) [E]

From: McKinnie, Carolyn - APHIS <Carolyn.J.McKinnie@aphis.usda.gov>
Sent: Friday, May 12, 2017 3:04 PM
To: Morse, Brent (NIH/OD) [E]
Subject: SNBL Everett Washington
Attachments: SNBL USA Ltd (R) 5-1-17.pdf

Hi Brent,
Good talking to you today. Please see the attached. Let me know if you have any questions.
Thanks, Carolyn

Carolyn J McKinnie, DVM
USDA APHIS Animal Care
Supervisory Veterinary Medical Officer
Pacific Northwest, Alaska, Guam, Saipan
Montana, Idaho, Utah, North & South Dakota
Phone Number cell
carolyn.j.mckinnie@aphis.usda.gov

USDA

United States Department of Agriculture
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Inspection Report

Snbl Usa Ltd
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Customer ID: **11124**
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STEVE GLAZA VIA EMAIL

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experience unrelieved pain or distress and such justification must be approved by the IACUC.

Unless such approved justification exists, an animal that can be reasonably be expected to experience more than slight or momentary pain and/or distress like these animals must receive analgesics, anesthetics and/or or other interventions appropriate to the nature and severity of the pain, discomfort or distress. Such methods of relief must be approved by the IACUC.

Correct from this time forward.

2.33(e)(5) CRITICAL REPEAT

ATTENDING VETERINARIAN AND ADEQUATE VETERINARY CARE.

In a protocol involving non-human primates, one of the monkeys sustained a fracture of the two long bones of the left forearm. Although lack of use and favoring of the affected limb was noted by facility personnel on two separate occasions on two days, the veterinarian was not contacted until approximately 19-20 hours after the first such observation. This monkey was subsequently euthanized shortly after veterinary examination. Fractures cause pain, which can be quite severe depending upon the location and severity of the fracture. While the fracture was unanticipated, the lack of reporting caused this animal to experience pain longer than had it been reported to the veterinary staff when initially noticed.

In a protocol involving full-thickness irradiation of guinea pigs, the approved protocol stated that pain or distress was not anticipated (despite categorization of the majority of animals as Category D) but pain relief would be provided if deemed necessary upon veterinary assessment. Forty (40) animals experienced outcomes (partial to full-thickness skin loss of skin caused by the irradiation) that could reasonably be expected to cause more than slight or momentary pain and/or distress. Of these, ten (10) animals were treated with buprenorphine.

In the event that unexpected pain or distress would occur in an animal, the attending veterinarian must be promptly contacted to assure expedient and appropriate action is taken to alleviate the pain, distress or discomfort. The affected animal must receive analgesics, anesthetics or other interventions appropriate to the nature and severity of the pain, discomfort or distress.

2.38(f)(1) CRITICAL REPEAT

MISCELLANEOUS.

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FORBES DIANE, D V M USDA, APHIS, Animal Care

Date: 05-MAY-2017

Title: VETERINARY MEDICAL OFFICER 5053

Received By:

STEVE GLAZA VIA EMAIL

Title: INSTITUTIONAL OFFICIAL

Date: 05-MAY-2017

Inspection Report

On 06 February 2017, a cynomolgus macaque on a study protocol received fractures of the radius and ulna.

On that morning, the monkey received a baseline neurological/musculoskeletal evaluation with no abnormalities detected. Blood was then collected minutes later for two separate evaluations. Approximately two-and-a-half hours later, the monkey was restrained for administration of a test article. All animal handling was conducted using a procedure box, to which it had been previously acclimatized.

Observation of the animal on a scheduled neurological/musculoskeletal evaluation conducted approximately four hours post-dose indicated that it could grasp with the left hand when the squeeze back was used, but not using that hand when left alone. Clinical observations approximately one hour later indicated bruising of the right lower forelimb and right hind limb, as well as a scab/crust of an upper hind limb.

Scheduled clinical observations and neurological/musculoskeletal evaluation the next morning were consistent with those on the previous day. An unscheduled clinical observation was performed approximately 20 hours after the first abnormal neurological/musculoskeletal evaluation. This observation included consistent results as previous observations but included swelling of the lower left forelimb.

A veterinary examination was conducted within minutes of this latter observation, which indicated no use of the left arm, mild swelling to the forearm, with a planned sedation for x-ray and limb palpation. This latter evaluation revealed displaced fractures of the radius and ulna. The monkey was then euthanized. The veterinary assessment was conducted approximately 20 hours after the initial abnormal observation due to lack of reporting to the veterinary staff.

While the exact cause of the fractures was not determined by the test facility, the "Animal Welfare Incident Report" submitted to the facility Institutional Animal Care and Use Committee stated that "the injury most likely occurred during the Feb. 6th blood collection and/or dosing."

The test facility must assure that the handling of all animals is conducted as expeditiously and carefully as possible in a manner that does not cause trauma, overheating, excessive cooling, behavioral stress, physical harm, or unnecessary discomfort.

During this inspection, it was noted that the test facility has enacted a number of improvements with regards to the welfare, training and behavior and environmental enhancements since the last inspection. These changes include a re-organization to align husbandry, study and veterinary staff under one cohesive line of management and improved

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observation and tracking of behavioral conditions.

This inspection and exit briefing were conducted with facility representatives.

Additional Inspectors

Schnell Michael, Veterinary Medical Officer

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