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

April 12, 2017

Re: Animal Welfare Assurance
#A3086-01 (OLAW Case E]

Wendeline L. Wagner, DVM
IACUC Chair
Bioqual
12301 Parklawn Drive
Rockville, MD 20852

Dear Dr. Wagner,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your March 3, 2017 letter reporting an adverse event involving nonhuman primates at Bioqual, Inc., following up on an initial report on August 8, 2016. According to the information provided, OLAW understands that a total of eight African Green monkeys died within the course of a day following a bronchioalveolar wash and blood sampling under anesthesia. The monkeys were on an approved protocol, had received an experimental compound that was considered safe, were subjected to procedures which had been safely performed numerous times before, were handled by trained staff, and recovered uneventfully from anesthesia. Seven animals were subsequently found dead and one was found in respiratory distress and was unsuccessfully treated. Some of the animals were in the control group and therefore the vehicle in the compound was evaluated.

The study was placed on hold awaiting pathology and toxicology results. The pathology report indicated no sign of trauma or infectious disease. Because no cause of death could be identified, the Institutional Animal Care and Use Committee (IACUC) approved a request to repeat the study. This was done in a different building with different staff, animal body weight and temperature was monitored at anesthesia, weight loss greater than 10% had veterinary intervention as needed, there was more post-anesthesia monitoring, and if all lung wash fluid was not recovered the veterinarian would intervene. The veterinary technicians had been retrained on the lavage technique, and adverse event documents were reviewed and approved by the IACUC. The repeated study was performed without incident.

Based on its assessment of this explanation, OLAW understands that although no cause of death was found, measures were taken which successfully prevented recurrence of the problem. OLAW concurs with the actions taken by the IACUC to comply with the PHS Policy on Humane Care and Use of Laboratory Animals.

Sincerely,

(b) (6)

Axel Wolff, M.S., D.V.M.
Director
Division of Compliance Oversight

cc: Mark Lewis, Ph.D., Institutional Official
Elizabeth Goldentyer, D.V.M., Eastern Regional Director, USDA-APHIS-AC

A3086-E

Wendeline L. Wagner, DVM

IACUC Chairperson

BIOQUAL, Inc

12301 Parklawn Drive

Rockville, MD 20852

301-881-8824

F 301-881-9175

03 March 2017

Neera V. Gopee, DVM, PhD, DACLAM, DABT

Animal Welfare Program Specialist

Division of Compliance Oversight

Office of Laboratory Animal Welfare

National Institutes of Health

Dear Dr Gopee:

In response for the request for follow up concerning the adverse event report of August 2016, for BIOQUAL protocol 16-054, I have the following resolution.

29 November 2016 USDA focused inspection (report attached to e-mail)

9 December 2016 BIOQUAL IACUC special meeting to

(1) review original protocol (16-054) and subsequent reports
    a. extensive pathology reports from two different organizations
        i. both reports conclude no sign of infectious disease or trauma
    b. analysis of fluid used for bronchio-alveolar lavage
        i. fluid is Phosphate Buffered Saline (PBS) with no contaminants found
(2) update committee on USDA inspection and act on requirements
    a. IACUC Policy 15 defining Adverse Events and expectations is drafted
    b. Lab Form 052 for reporting Adverse Events is refined
(3) Full Committee review on new protocol 16-105P
    a. The IACUC voted unanimously to approved 16-105P which requests to repeat the study (16-054) with these updates

i. The protocol work was placed in a different BIOQUAL animal facility than 16-054, with different staff
ii. The requested work requires that non-human primates have body temperature and weight monitored at every anesthesia time point, and if weight drops by more than 10% a veterinarian will be contacted and intervention will be started
iii. The primates on the study will have more monitoring time points after anestesia
iv. Per revised SOP, if BAL fluid is not fully recovered from any animal, the veterinarian is immediately contacted for veterinary intervention

b. Veterinary technical staff involved in 16-054 were re trained on broncho-alveolar lavage procedures

27 December 2016 BIOQUAL IACUC special meeting to finalize documents

(1) IACUC Policy 15 Adverse Event was approved by all members, and signed
(2) Lab Form 052 Rev 1 Adverse Event Description (report form) was reviewed and approved

10 February 2017 BIOQUAL IACUC quarterly meeting (regularly scheduled)

(1) Report to IACUC on replacement protocol 16-105P, which was completed without incident

Thank you for your concern and follow up. If you have any further questions, please contact me.

Wendeline L. Wagner, DVM

Gopee, Neera (NIH/OD) [E]

From: Gopee, Neera (NIH/OD) [E]
Sent: Friday, March 03, 2017 11:04 AM
To: 'Wendy Wagner'
Subject: RE: Follow Up on OLAW preliminary report for Animal Welfare Assurance #A3086-01 Case E

Dear Dr. Wagner,
Thank you for this interim report, we look forward to receiving the final detailed report signed by the Institutional Official in the near future.

Neera

From: Wendy Wagner [mailto:wwagner@bioqual.com]
Sent: Friday, March 03, 2017 10:38 AM
To: Gopee, Neera (NIH/OD) [E] <neera.gopee@nih.gov>
Subject: RE: Follow Up on OLAW preliminary report for Animal Welfare Assurance #A3086-01 Case E

Below is a brief outline of events since the report I sent you in August of 2016.

Attached are the USDA focused inspection report, a more detailed report concerning the adverse event, and our internal Adverse Event reporting documents.

Please feel free to contact me if you need any more information.

WW

29 November 2016 USDA focused inspection (report attached to e-mail)
9 December 2016 BIOQUAL IACUC special meeting to
(1) review original protocol (16-054) and subsequent reports
(2) update committee on USDA inspection and act on requirements
(3) Full Committee review on new protocol 16-105P (to repeat the study)

27 December 2016 BIOQUAL IACUC special meeting to finalize documents
(1) IACUC Policy 15 Adverse Event
(2) Lab Form 052 Rev 1 Adverse Event Description

10 February 2017 BIOQUAL IACUC quarterly meeting (regularly scheduled)
(1) Report to IACUC on replacement protocol 16-105P, which was completed without incident

WW

Wendeline L Wagner, DVM
IACUC Chair
BIOQUAL, Inc
(b) (6)

From: Gopee, Neera (NIH/OD) [E] [mailto:neera.gopee@nih.gov]
Sent: Thursday, March 2, 2017 2:27 PM
To: Wendy Wagner <wwagner@bioqual.com>
Subject: RE: Follow Up on OLAW preliminary report for Animal Welfare Assurance #A3086-01 Case E

Thank you Dr. Wagner for the prompt response and I look forward to receiving your report.

Neera

From: Wendy Wagner [mailto:wwagner@bioqual.com]
Sent: Thursday, March 02, 2017 2:22 PM
To: Gopee, Neera (NIH/OD) [E] <neera.gopee@nih.gov>
Subject: RE: Follow Up on OLAW preliminary report for Animal Welfare Assurance #A3086-01 Case E

A report was just given at our quarterly IACUC meeting on February 10, 2017; in addition we recently had a follow up USDA visit concerning this.

I will supply OLAW with these details tomorrow.

Thank you,

WW

Wendeline L Wagner, DVM
IACUC Chair
BIOQUAL, Inc
(b) (6)

From: Gopee, Neera (NIH/OD) [E] [mailto:neera.gopee@nih.gov]
Sent: Thursday, March 2, 2017 2:14 PM
To: wwagner@bioqual.com
Subject: Follow Up on OLAW preliminary report for Animal Welfare Assurance #A3086-01 Case E

Dear Dr. Wagner,

I am writing with regards to an adverse event which was reported by you via email on August 9, 2016 involving mortalities in African Green Monkeys at BIOUAL, Inc. To date, we do not have a record of receiving further information regarding this preliminary report. If there is a final or interim report available, please forward it to the OLAW Division of Compliance Oversight (NIH/OD) olawdco@od.nih.gov . If you have any questions of concerns, please do not hesitate to contact our Office.

Thank you.

Regards,
Neera

Neera V. Gopee, DVM, PhD, DACLAM, DABT
Animal Welfare Program Specialist

Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

A3086-E

USDA

United States Department of Agriculture
Animal and Plant Health Inspection Service

INSPECTION REPORT

cust_id
insp_id
site_id

BIOQUAL INC
4 RESEARCH COURT

ROCKVILLE, MD 20850

Customer ID: 93
Certificate: 51-R-0036

Site: 003
BIOQUAL INC
Inspection
Type: Routine
Date: 29 November 2016

2.33 (b)(5)

***On August 2, 2016 three (3) African Green Monkeys on study 16-054 died following a bronchial alveolar gavage procedure. One (1) was found dead and the other two were in respiratory distress and expired after unsuccessful attempts to revive them. The following day, August 3, 2016, five (5) additional African Green Monkeys on the study were found dead during the morning health check. Four (4) African Green Monkeys on the study remain and have not demonstrated any signs of illness or distress.

Post-procedural monitoring was conducted per SOP during normal work hours, however no additional monitoring of the remaining nine (9) non-human primates on the study was conducted overnight. Due to the recent deaths of the non-human primates on study, more frequent monitoring may have allowed for more immediate intervention to prevent the deaths of the remaining animals on the study. Procedures must be established and implemented to ensure adequate monitoring of study animals following an adverse event. Correct by December 30, 2016.

Prepared By: (b) (6) **Date:** 30-NOV-16
MCFADDEN, GLORIA S - APHIS, USDA, APHIS, Animal Care
Title: VETERINARY MEDICAL OFFICER **Inspector ID:** 1048

Received By: (b) (6) **Date:** 30-NOV-16
WENDY WAGNER
Title: DIRECTOR & IACUC CHAIR

BIOQUAL, Inc.	IACUC Policy	
TITLE: **Adverse Event**		Page 1 of 3
Policy No. : IP-015-00	Supersedes: New	Implementation Date: 27 December 2016
Reference: US Food and Drug Administration		Next Review Date: 02 January 2020
Prepared By/ Date: (b) (6) W. WAGNER	Reviewed and Approved By/ Date:	(b) (6)

POLICY STATEMENT

Adverse Event Definition:

At BIOQUAL, an Adverse Event is an unexpected medical occurrence in a research animal(s) and this event is not specifically approved on a BIOQUAL IACUC approved protocol. The Adverse Event is an unintended finding, clinical sign or disease process resulting in harm or death to animals caused by:

a) research test article, vaccines and/or research process / procedures

b) employee mishandling of animals, misconduct, negligence or dereliction of duty

c) facility failure or malfunctions such as fire, flood, HVAC or other mechanical failures, loss of potable water supply

d) natural disasters, environmental emergency, terrorism, or others

There are gradations of Adverse Events, ranging from mild to fatal. Mild and Moderate reactions are immediately reported to the clinical veterinarian for any required treatment and are recorded in the animal record. Serious and fatal adverse events are to be reported to the IACUC using Laboratory Form 54 as soon as possible, but no later than 72 hours after the occurrence.

Mild Adverse Event: Transient or mild discomfort of less than 48 hours duration; no veterinary intervention or therapy required.

Moderate Adverse Event: Mild to moderate discomfort or limitation in activity; minimal veterinary intervention or therapy required.

Serious Adverse Event: Serious adverse event is a major clinical illness that is life threatening and could result in a persistent or significant disability or incapacity if untreated; veterinary care and/or treatment along with increased monitoring is required, as is potential removal from study.

Fatal Adverse Event: Fatal Adverse Event is any event that causes immediate death for the experimental animal, unexpected death within 72 hours of a procedure, or health complications so severe that euthanasia is required within 7 days of the adverse event.

Adverse Event Procedure:

Mild and Moderate Adverse Events, must be reported to the clinical veterinarian the same day as discovered. A description of the clinical findings and any treatment will be recorded in the animal record and will be relayed to the Principal Investigator.

Serious and Fatal Adverse Events, must be immediately reported to the clinical veterinarian and BIOQUAL Principal Investigator and reported within 72 hours to the IACUC using BIOQUAL Lab Form No. 054, Adverse Event Report. This form is to be completed by the Principal Investigator, Veterinarian or Project Manager but the signature of the clinical veterinary is required.. All relevant laboratory, pathology or other reports are to be included or summarized on Form 054. Follow up information should be forwarded to the IACUC as it becomes available.

Following the discovery and subsequent report of a Serious or Fatal Adverse Event, increased monitoring of the surviving animal (s) on the entire study, and any related study (as determined by the IACUC and/or Attending Veterinarian) will be required. This increased monitoring is required with the exact parameters tailored by the facility veterinarian for the clinical situation, but will include attention to the following issues:

1) Protocol review / evaluation by IACUC or IACUC subcommittee, Principal Investigator and Veterinarian.

2) Increased monitoring time points for animals identified with Adverse Events and also for animals on the same (and similar) studies that have not yet shown clinical signs.

3) Increased laboratory monitoring for animals identified with Adverse Events and also for animals on the same (and similar) studies.

4) Situation specific corrective actions (staff retraining, enacting Disaster Protocols, mechanical repairs)

5) Duration and type of the actions are at the professional judgement of the clinical veterinarian unless or until the IACUC makes a determination regarding the outcome of the animal(s) and/or protocol.

END OF DOCUMENT

BIOQUAL, Inc.

Adverse Event Description

IACUC Proposal ID No.		Date Identified	
Animal ID		Species	
Project Investigator		Study Title	
Location of Event (Facility and Room #)			
Outcome	☐ Treated / Recovered	☐ Euthanized	☐ Fatal

1. Provide a description (include dates and details) of the adverse event or unexpected outcome:

2. Provide a description of the corrective actions taken to ensure that this type of event or unexpected outcome does not reoccur:

Submitted by: _____ _____

Printed Name and Signature — Date

Reviewed by: _____ _____

Veterinarian Printed Name and Signature — Date

BIOQUAL, Inc.

Adverse Event Description

3. IACUC Action and Resolution:

IACUC Chair: _____ _____

Printed Name and Signature | Date

A3086-E

BIOQUAL, Inc.

BIOQUAL Institutional Animal Care and Use Committee
12301 Parklawn Drive
Rockville Maryland 20852
301-881-8824 (f) 301-881-9175

Monday, August 8, 2016

Director 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

RE: Adverse Event Report
D16-00052 (A-3086-01)

The BIOQUAL, Inc Institutional Animal Care and Use Committee chairperson received a report of an unexpected event on BIOQUAL animal use proposal **16-054**, with title **'Evaluation of a Candidate Therapeutic in the African Green Monkey Model of Respiratory Syncytial Virus (RSV) Infection'**. This protocol was approved for the use of 12 African Green monkeys (*Chlorocebus sp*) to test a proprietary therapeutic compound for effectiveness against Respiratory Syncytial virus infection. The compound had been safety tested in cynomolgus macaques previously. At a sample time point that was approximately 30 days after the last dose of the experimental compound, all 12 animals were anesthetized and blood and bronchioalveolar wash samples were obtained per BIOQUAL SOP. These samples had been collected multiple times from these animals previously using the same anesthesia, by the same technician, with no difficulties. The 12 African Green monkeys of this report were observed to awaken from anesthesia and appear normal. A short time later, two of the animals were found deceased and a third was in respiratory distress and was transported to the intensive care unit and placed in an oxygen support cage. Later, this third animal died. The remaining nine animals appeared normal at the end of the work day. The following morning, 5 animals were found deceased. A total of 8 animals on the study of 12 died within one day.

The facility veterinarian, performed a necropsy on each of the 8 animals, and samples were submitted for pathology, these results are pending. Gross examination revealed pulmonary edema along with mild liver and kidney changes which may have been post mortem changes.

The animal deaths included individuals from the vehicle control group. The several weeks from the last dose and the inclusion of animals that had never been dosed leads to the thought at this time the experimental drug would not be implicated. However the vehicle is being evaluated for possible toxicity. That conclusion is pending.

The animal housing did not appear to be at fault. The animals were housed in biocontainment caging, which was all functioning normally and is routinely inspected and is certified at least annually. The animal room environmental conditions were within GUIDE recommendations.

The animal technician that performed the procedure was experienced and proficient; and had successfully performed the procedures in the past. There is documentation on this training.

This animal use proposal, 16-054, is currently ON HOLD with the BIOQUAL IACUC, and will remain ON HOLD until a cause of death can be documented and a plan to prevent a future similar occurrence can be put in place.

A follow up report will be sent when we have further information.

Sincerely

(b) (6)

Mark G Lewis, PhD
Institutional Official
President, CEO
BIOQUAL, Inc

(b) (6)

Wendeline L. Wagner, DVM
IACUC Chairperson
Director, Parklawn Drive
BIOQUAL, Inc

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Wednesday, August 10, 2016 6:07 AM
To: 'wwagner@bioqual.com'
Subject: RE: BIOQUAL report D16-00052

Thank you for this preliminary report, Dr. Wagner. We will open a new case file.

Axel Wolff, M.S., D.V.M.
Director, Division of Compliance Oversight
OLAW

From: Dr. Wendeline Wagner [mailto:wwagner@bioqual.com]
Sent: Tuesday, August 09, 2016 11:02 AM
To: OLAW Division of Compliance Oversight (NIH/OD)
Subject: BIOQUAL report D16-00052

OLAW Division of Compliance Oversight:

Attached is a letter from BIOQUAL, Inc (Assurance D16-00052/A-3086-01) with a report of an adverse event on one animal use proposal that resulted in the unexpected death of eight African Green Monkeys in an 18 hour period of time. This animal use proposal, 16-054, has been placed on hold and an investigation is on-going while toxicology and pathology reports are pending. When the report is final, and update will be sent to you with those findings and with the final recommendations of the IACUC.

If you have any further questions or comments, please feel free to contact me.

Thank you,

WW

Wendeline L. Wagner, DVM
IACUC chair
Director, Parklawn Drive
BIOQUAL, Inc
12301 Parklawn Drive
Rockville, MD 20852
(b) (6)