



DEPARTMENT OF THE ARMY
HEADQUARTERS, U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
810 SCHREIDER STREET
FORT DETRICK, MARYLAND 21702-5000

May 28, 2019

(b) (6)

Director of Quality and Compliance
Biomere Facility

(b) (6)

Worcester, MA 01608

Dear (b) (6)

(b) (6) Executive Officer, and (b) (6) Manager, Animal Care and Use Review Office, Office of Research Protections, U.S. Army Medical Research and Development Command, conducted a site visit to the Biomere Facility on 10 May 2019 to evaluate the animal care and use program and the animal care facilities. Participating individuals and results of the site visit are outlined in the enclosed checklist. Suggestions for improvement are offered in the absence of regulatory or guideline standards. These "best practices" are methods the staff observed to work well within other programs/facilities and are offered for the institute's consideration.

This AAALAC International-Accredited Animal Care and Use Program is compliant with federal Animal Welfare Regulations and the recommendations of the Guide for the Care and Use of Laboratory Animals (Institute for Laboratory Animal Research).

While compliant with applicable regulations, the institution does need to increase focus on ensuring operations match policy. In many cases, written policies are not fully implemented in daily operations within the animal care and use program. While not necessarily in violation of regulations, this circumstance may create confusion on appropriate animal care practices, can lead to regulatory noncompliance, and impedes accurate external evaluation of the program.

The Animal Care and Use Review Office recommends continued funding of the supported animal research to appropriate Department of Defense agencies.

The point of contact for this action is the undersigned at (b) (6) or (b) (6)

Sincerely,

(b) (6)

Director, Animal Care and
Use Review Office

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Enclosure

CC (w.encl):

(b) (6), Protocol PI
(b) (6), Award PI
(b) (6), Attending Veterinarian
(b) (6), COR
(b) (6), Science Officer
(b) (6), Contract Specialist



COMPONENT OVERSIGHT OFFICE (COO) VISIT CHECKLIST

| | | | |
|-------------------|-------------|-----------------------|--------------------------------|
| Site/Visit Type: | Site Visit | Site Visited: | Biomere Facility |
| Date(s) Of Visit: | 10 May 2019 | Award and Protocol #: | (b) (4) |
| Award PI Name: | (b) (6) | Awarded Organization: | Massachusetts General Hospital |
| Funding Agency: | CDMRP | Species Approved: | Nonhuman primates |
| Protocol PI Name: | (b) (6) | Site Visitors: | (b) (6) |
| Protocol Title: | (b) (4) | | |

I. Names and titles of personnel present at in- and out-brief:

| NAME | TITLE OR DEPARTMENT |
|---------|------------------------|
| (b) (6) | Institutional Official |
| | Attending Veterinarian |
| | Protocol PI |
| | CEO |
| | President |

II. IACUC Membership and Function:

| | A | MD | SD | N/A |
|---|---|----|----|-----|
| a. Appropriate constitution (at least 5 required members, or 3 required members if not PHS Assured) | X | | | |
| b. Non-affiliated members (NAM) attend meetings regularly | X | | | |
| c. Member appointments available and current | X | | | |
| d. IACUC member training program in place | | X | | |
| e. Appropriate documentation of IACUC training for all members to include alternates | | X | | |
| f. Mechanism in place for reporting welfare concerns | X | | | |
| g. IACUC function document (SOP/Policy/Instruction) | | X | | |
| h. Instructions for reporting concerns prominently displayed throughout the facility | X | | | |
| i. Reported concerns were well investigated by the IACUC | | X | | |

¹ A-acceptable

MD- minor deficiencies

SD- significant deficiencies



COMPONENT OVERSIGHT OFFICE (COO) VISIT CHECKLIST

| | | | | |
|---|--|---|--|---|
| j. Adverse events, violations, and animal welfare concerns reported to COO and documented in file | | X | | |
| k. If part-time AV, written program of veterinary care including regularly scheduled visits to the facility | | | | X |

Comments:

d-e: Training records are incomplete, don't match policy requirements, and are maintained in various different ways, making it extremely difficult to conduct a comprehensive review and determine if required training is being completed. The institution needs to evaluate training policies and regulatory training requirements to determine if the program meets those requirements as well as the institute's needs. Completion of required training can best be assessed when it is documented in one location that is easily accessible. In summary, the institute must develop a system by which the IACUC can ensure that staff and committee members have met all training requirements.

g. This document is in need of update in the following areas:

- Include specific details on the DMR process for (b) (4). This process is not described in any of the institutional documents.
- Update the language for full committee review to accurately reflect practice. As written, the language suggests that any protocol involving USDA regulated species is automatically referred to full committee review. This does not reflect current practice.
- The description of protocol suspension should describe reporting requirements to the USDA, funding agencies, and AAALAC International.
- The amendment section references 'withholding analgesia' as a potential amendment that could be reviewed via Veterinary Verification and Consultation; however, discussion with staff present at the exit brief revealed that this is not current practice
- The policy on significant changes is silent on the subject of animal numbers; since this is a common need for modification of a protocol, it should be included in the policy

i-j. During the evaluation of lab files, it was revealed that protocol deviations are not universally required to be submitted to the IACUC; the PI decides whether to submit. This practice must be changed and procedures for such reporting defined in IACUC policy. During the exit brief, there was discussion that some deviations may be related to GLP practices that are very specifically identified. Site visitors recommended that the institute consider separating the IACUC protocol from the GLP study plan to eliminate the need for small changes or changes not involving animals to be considered protocol deviations. Without this procedure in place, all deviations must be reported to the IACUC for evaluation, and reported to funding agencies and AAALAC, as required.

III: IACUC Minutes and Protocol Review:

| | A | MD | SD | N/A |
|---|---|----|----|-----|
| a. Attendance records maintained either in minutes or elsewhere | X | | | |



COMPONENT OVERSIGHT OFFICE (COO) VISIT CHECKLIST

| | | | | |
|--|---|--|--|---|
| b. Quorum present at each meeting | X | | | |
| c. Minutes demonstrate IACUC business other than protocol review | X | | | |
| d. Documentation in minutes or elsewhere of protocol review details | | | | X |
| e. Dissenting opinions included and explained | X | | | |
| f. IACUC documents and protocol records maintained for at least 3 years | X | | | |
| g. Protocols contain sufficient detail | X | | | |
| h. Annual protocol reviews conducted and documented | X | | | |
| i. Scientific justification for exceptions to AWARs and the Guide present in applicable protocols | X | | | |
| j. COO approval documents included in protocol files | X | | | |
| k. Appropriate keywords used for databases searched | X | | | |
| Dates of minutes reviewed: October 2018, January 2019, April 2019 | | | | |
| Comments: d. No full committee review meeting minutes were provided for review so it wasn't possible to determine if minutes of those meetings captured deliberations of the IACUC as required by the Animal Welfare Regulations. General comment: The minutes each include text indicating that the PI clarified that x number of protocols expired. This language is confusing, particularly when there are typographical errors as in the April minutes. Since reporting this information is not a regulatory requirement, consider removing it. | | | | |

IV: Semi-Annual Facility Inspection and Program Review (FIPR):

| | A | MD | SD | N/A |
|---|---|----|----|-----|
| a. FIPRs conducted and reports generated at least every six months | X | | | |
| b. At least two members participated in every area of the FIPR | X | | | |
| c. Non-affiliated member participation | X | | | |
| d. Deficiencies appropriately classified as minor or significant | X | | | |
| e. Report includes a reasonable and specific plan for correction of each deficiency with correction deadlines | | X | | |
| f. Individual responsible for correction of each deficiency identified | X | | | |
| g. Report identifies all locations visited during the facility inspection and areas of the program reviewed | | X | | |
| h. Departures from the provisions of the AWARs and the Guide are identified and justified | | X | | |



COMPONENT OVERSIGHT OFFICE (COO) VISIT CHECKLIST

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|---|---|--|--|--|
| i. Minority opinions are addressed | X | | | |
| j. Reports are signed by majority of IACUC members | X | | | |
| k. Documentation indicating reports are forwarded to IO | X | | | |

Dates of FIPR reports reviewed: April 2018, October 2018, April 2019

Comments:

e. The tracking of deficiencies is inconsistent. In several cases, deficiencies are noted with no plan for correction provided. In addition, comments captured on the OLAW checklist are not identified in the correction plan. There are numerous inconsistencies between the reports, checklists, and correction plans. The reports all indicate that there are no program deficiencies, yet one of the checklists indicates that there were concerns by at least one member about the depth of member training and a response is provided. However, this isn't reflected in the checklist itself and isn't identified in the correction plan as a deficiency. All of the checklists indicate that there are no minor deficiencies and yet both the reports and correction plans clearly identify multiple deficiencies. Each document used to make up the FIPR must be consistent in identifying all deficiencies, both programmatic and facility related.

g. Other than a brief statement in each report that there were no programmatic deficiencies, there is no indication that any depth of program review has occurred. The Committee must evaluate all areas of the animal care and use program and assess the quality of that evaluation on a semi-annual basis. This includes reviewing institutional policies, and the documentation of execution of those policies. It was apparent from the site visitors' review that no real evaluation of training or institutional policies has occurred. This must be rectified. Many resources exist to provide guidance on conduct of an appropriate program review. We highly recommend that the institute seek those resources and provide additional training to IACUC members on semi-annual program review.

h. An extensive list of approved departures is attached to the FIPRs. Many of these departures should be re-evaluated for scientific validity to ensure they are all adequately justified and aren't implemented solely for convenience.

V: General:

| | A | MD | SD | N/A |
|---|---|----|----|-----|
| a. Up-to-date listing of all SOPs, including most recent review date in accordance with SOP | X | | | |
| b. Comprehensive Disaster Plan in place that covers animal disposition and prioritization? | | X | | |
| c. Disaster Plan identifies essential personnel | | X | | |
| d. Disaster Plan part of the institution's overall emergency response program | | X | | |
| e. Comprehensive occupational health and safety (OHSP) plan in place | X | | | |

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COMPONENT OVERSIGHT OFFICE (COO) VISIT CHECKLIST

| | | | | |
|--|---|---|--|---|
| f. All staff members, to include contractors, evaluated as part of the OHSP. If not, procedures are in place to ensure individuals not included in the OHSP have alternative means of evaluation | | X | | |
| g. Acceptable Psychological Well-Being Plan for NHPs in place, if applicable | X | | | |
| h. Acceptable Exercise Plan for Dogs in place, if applicable | | | | X |
| i. Environmental Enrichment Plan covers for all species | X | | | |
| j. Mechanism in place to assure all protocol personnel have been trained to perform their role | X | | | |
| k. Training records match the training requirements of the institution and IACUC | X | | | |

Comments:

b-d. While the plan identifies a multitude of possible disaster scenarios, there are very few details provided on implementation of disaster responses, including essential personnel, interaction with local emergency services, and animal disposition. These areas should be clearly described and trained to Biomere staff so that responses are second nature. As written, little clear instruction exists. Additionally, as was the case in other program documents reviewed, policy outlined procedures that are not currently in practice - generators are not tested on a monthly basis and week of potable water supply is not currently on site as indicated in the policy. No information regarding euthanasia supplies is provided nor are the individuals responsible for the decision to euthanize or for carrying out these procedures identified.

f: While a requirement for negative TB test and measles titers were communicated to the site visitors ahead of the visit, no request for documentation of these tests were required prior to entry to the animal facility. The institution should ensure policies in place are consistently followed for occupational health evaluation of personnel entering the facility.

V. FUNDED ANIMAL WORK:

| EXTRAMURAL SITES ONLY | A | MD | SD | N/A |
|---|---|----|----|-----|
| a. Observed animal procedures are being performed as reviewed and approved by ACURO | X | | | |
| b. All personnel performing animal procedures approved in the IACUC protocol | X | | | |
| c. All changes to the protocol been reviewed and approved by the local IACUC | | | | X |
| d. All changes to the protocol been approved by ACURO | | | | X |
| Comments: None. | | | | |

VETERINARIAN REVIEW:

| I. PHYSICAL ENVIRONMENT | A | MD | SD | N/A |
|--|---|----|----|-----|
| a. Microenvironment and Macroenvironment | X | | | |

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COMPONENT OVERSIGHT OFFICE (COO) VISIT CHECKLIST

| | | | | |
|-----------------------------|---|--|--|--|
| b. Housing | X | | | |
| c. Space Recommendations | X | | | |
| d. Temperature and Humidity | X | | | |
| e. Ventilation | X | | | |
| f. Illumination | X | | | |
| g. Noise/Vibration | X | | | |

Comments:

General comments: The animal facility was clean and well maintained. It was clear that company leadership has been willing to invest in creating a high quality facility that has been well maintained by a highly effective complement of staff. Furthermore, key systems have been installed with appropriate redundancy (e.g., chillers, boilers, generators) in order to ensure continuity of operations during any equipment outages. All staff were knowledgeable and demonstrated dedication to program improvement and achieving a high level of animal welfare.

| II. BEHAVIORAL MANAGEMENT | A | MD | SD | N/A |
|---------------------------|---|----|----|-----|
| a. Structural Environment | X | | | |
| b. Social Environment | X | | | |
| Comments: None. | | | | |

| III. HUSBANDRY | A | MD | SD | N/A |
|---|---|----|----|-----|
| a. Food | | X | | |
| b. Water | X | | | |
| c. Bedding | X | | | |
| d. Sanitation | X | | | |
| e. Waste Disposal | X | | | |
| f. Pest Control | | X | | |
| g. Emergency, Holiday, and Weekend Care | X | | | |

Comments:

a. Animal feed is received from vendors, but there are no procedures for regular verification of feed quality testing. The Guide (pg. 66) recommends regularly soliciting feed testing documentation from feed vendors to ensure feed quality. The institution should implement procedures to verify quality of feeds provided to research animals.

f. Live rodent traps are used in some parts of the facility, but placement of traps was inconsistent (b) (4) Daily checks of traps are conducted, but documentation of daily checks was not available. There was no documentation of the types and numbers of pests observed in the facility. Recommend a review of pest control program and its implementation to ensure pest control and monitoring is carried out in accordance with institutional policies.

| IV. POPULATION MANAGEMENT | A | MD | SD | N/A |
|-------------------------------|---|----|----|-----|
| a. Identification and Records | X | | | |



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| | | | | |
|--|---|--|--|--|
| b. Genetics and nomenclature | X | | | |
| Comments: General comments: The behavioral and environmental enrichment program for NHPs was well designed, detailed, well executed, and appeared to be very effective in improving well-being of the primates housed in the facility. | | | | |

| V. ANIMAL PROCUREMENT AND TRANSPORTATION | A | MD | SD | N/A |
|---|---|----|----|-----|
| a. Quarantine, Stabilization, and Separation | X | | | |
| b. Surveillance, Diagnosis, Treatment, and Control of Disease | X | | | |
| Comments: None. | | | | |

| VI. VETERINARY MEDICAL CARE | A | MD | SD | N/A |
|------------------------------------|---|----|----|-----|
| a. Preventive Medicine | X | | | |
| b. Surgery | X | | | |
| c. Facilities for Aseptic Surgery | X | | | |
| d. Pain, Analgesia, and Anesthesia | X | | | |
| e. Euthanasia | X | | | |
| Comments: None. | | | | |

| VII. FUNCTIONAL AREAS | A | MD | SD | N/A |
|---|---|----|----|-----|
| a. Corridors | X | | | |
| b. Animal Room Doors | X | | | |
| c. Exterior Windows | X | | | |
| d. Floors | | X | | |
| e. Drainage | X | | | |
| f. Walls | X | | | |
| g. Ceilings | X | | | |
| h. Heating, Ventilation, and Air Conditioning (HVAC) | X | | | |
| i. Power and Lighting | X | | | |
| j. Storage Areas | | X | | |
| k. Noise Control | X | | | |
| l. Facilities for Sanitizing Materials | | X | | |
| Comments: d. The floor of the freight elevator, which is used for movement of animals and equipment between floors of the vivarium, was damaged, resulting in accumulation of a significant amount of debris. Per the Guide (pg 72), cage wash areas should be regularly cleaned and disinfected based on usage and risk of contamination. Additionally, though the elevator is located outside the facility zone where PPE is used, current policies allow personnel to traverse the elevator from floor to floor without removal of PPE. The institution should assess PPE practices and evaluate procedures for cleaning and sanitation of the freight elevator or practices for movement of equipment and animals to minimize the risk of contamination of equipment moved thru that space. | | | | |



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j. The temperature in the short-term feed storage room was >70degF and the relative humidity in the main feed storage room was >50%. The Guide (pg 66) recommends feed be stored at temperatures < 70degF and <50% RH. The institution should evaluate the need for implementation of appropriate facility changes to ensure feed storage under appropriate environmental conditions or develop procedures to minimize the risk of deterioration of feed quality given current storage conditions.

j. Large numbers of animal cages and equipment are stored in the vivarium corridors, which impedes movement of equipment and adequate cleaning of floors and walls in corridors. Per the Guide (pg 141), "Adequate space should be available for storage of equipment, supplies, food, bedding, and refuse. Corridors are not appropriate storage areas." The institution should discuss and evaluate ways to minimize the need to store caging and other equipment in vivarium hallways.

l. Cage wash temperatures are verified using chemical indicator strips. However, there is no method in place for regular assessment of effectiveness of sanitation for items cleaned in the cage washer. The Guide (pg 73) recommends regular evaluation of sanitation effectiveness of equipment, including caging using appropriate methods (e.g., culture, ATP detection, artificial soil removal, etc.). The institution should develop and implement procedures for regular evaluation of effectiveness of cage wash sanitation.

l. The emergency shutoff switch for one of the cage washers was not clearly identified. Recommend current institutional policies be implemented to ensure that emergency shut of switches for cage washers are clearly identified.