Centers for Disease Control and Prevention
Response to December 1, 2005 AAALAC Letter

1. **Veterinary Oversight in the Biosafety Level (BSL)-4 areas:**

1.a. Lack of veterinary access to the BSL-4 areas was noted in the 2002 site visit. The CDC indicated adoption of U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) model for access control in the November 25, 2002 response to the 2002 site visit. Evidence of lack of involvement in the BSL-4 areas by the IACUC and veterinary staff suggested that the CDC had not followed the stated plan and commitment to resolve the deficiency.

1.a.1. A sufficient number of veterinarians, veterinary care staff and care technicians were not granted unaccompanied access to the BSL-4 suite by the June 2003 deadline as indicated in the November 25, 2002 letter to Council. Only two veterinarians had unaccompanied access, but one was prevented access to the suite due to 'technical difficulties'.

1.a.2. The viewing windows on the corridor for the BSL-4 east side were obstructed and prevented observation into the suite. Combined with the restrictive entrance policies, neither the veterinary staff nor the IACUC could assess animal well-being and care and use practices in the BSL-4 east side.

RESPONSE to 1.a.1. and 1.a.2.:

A letter of veterinary authority addressed to CDC investigators and signed by the Director of CDC, has been sent to formalize the [redacted] oversight of veterinary care and animal husbandry in all areas where laboratory animals are used, including the BSL-4 laboratories. [redacted] currently has two veterinarians with independent access to both sides of the BSL-4 suite. A third veterinarian must complete the final phase of training prior to receiving independent access to the suites. This training is expected to be completed within the first quarter of 2006. One additional ARB veterinarian has received the CDC required training and is available to enter the BSL-4 suite under escort. Additionally, two animal caretakers received independent access to the BSL-4 suite and are currently conducting husbandry duties on a daily basis. Three additional animal caretakers recently completed the ABSL-4 Science and Safety Training Program at Emory University, and will receive access to the BSL-4 suite after completion of CDC required training.

The IACUC has been actively working with senior management in the National Center for Infectious Diseases (NCID) and the research staff responsible for the BSL-4 facility to resolve the issues raised by AAALAC at the 2002 inspection. These meetings helped facilitate a resolution to the BSL-4 issues cited by AAALAC. These regular meetings have also led to a recognition by all involved of the importance of conforming to regulatory standards.

The following list identifies individuals with access to the BSL-4.

Name	Approval for Access to the BSL-4 (Select Agent Clearance)	Select Agent Risk Assessment Approval (FBI Clearance)	BSL-4 Laboratory Supervisor Approval (independent access)
[redacted]	August 8, 2005	May 4, 2005	IN TRAINING
[redacted]	August 8, 2005	November 12, 2003	APPROVED
[redacted]	April 22, 2004	October 15, 2003	APPROVED
[redacted]	November 10, 2004	November 10, 2004	IN TRAINING
[redacted]	October 11, 2005	October 24, 2003	APPROVED
[redacted]	October 11, 2005	October 23, 2003	APPROVED

1.a.3. The lack of reporting relationship between the technician hired by the BSL-4 Manager and the veterinary staff contributed to inadequate veterinary care and protocol non-compliance in a specific case of provision of fluids to a diseased animal.

RESPONSE:

Consistent with NCID recommendations that the [redacted] have full responsibility for husbandry for all animal areas at all Atlanta campuses, [redacted] (ARB) of SRP initiated husbandry support for the BSL-4 suites on December 6, 2005. Because we now have animal care staff working in the BSL-4 suites who report directly to the Attending Veterinarian, effective communications have been established to ensure all veterinary instructions for animal care are followed as directed. The ARB has sufficient staff to rotate caretakers into the BSL-4 to ensure appropriate care on a daily basis. This assignment reestablishes the reporting relationship from the animal health technician to the institutional veterinary oversight. The [redacted] technician no longer provides routine husbandry support for animals maintained in the BSL-4 except under special arrangement by the Attending Veterinarian.

1.a.4. Animal care technical back-up provisions consisted of only the BSL-4 Manager for weekends, holidays or emergencies.

RESPONSE:

All animal care responsibilities for the BSL-4 laboratory are now the responsibility of the ARB. Weekend, holiday, and emergency duties are

currently shared between two animal health technicians who report to the Attending Veterinarian and each has independent access to the BSL-4 suite, and three additional animal health technicians have completed initial training.

1.a.5. Animal records were not available to document proper oversight. When requested by site visitors, the BSL-4 Manager declined to provide access.

RESPONSE:

We regret the site visitors were denied access to records of animal care in the BSL-4 suite. This is unacceptable. We assure you that we will make these records readily available to AAALAC and to the Attending Veterinarian in the future.

2. Institutional Animal Care and Use Committee (IACUC) Oversight in the BSL-4 areas

2.a. Historically, the IACUC had been denied entry due to insufficient training to meet entry requirements.

2.b. No alternate methodologies were implemented (i.e. videotaped walk-through or view through windows).

RESPONSE to 2.a. and 2.b.:

We recognize that the IACUC oversight of the BSL-4 needs improvement. The nature of the work conducted in this area is such that safety has been the overriding imperative in deciding who is trained to go into the area, and CDC's policy has been that only those who are directly involved in doing the research should have access. As such, we have never considered training an IACUC member to enter just for inspection purposes. However, [redacted] provides veterinary support for the animal studies in the BSL-4, and he is an IACUC member. When animal experiments are being conducted in that environment, he reports on their progress to the IACUC. Indeed, in 2003, the IACUC suspended a very high profile smallpox experiment in non-human primates because the investigators were deemed not to have followed their protocol concerning the use of analgesics.

Although most members of the IACUC cannot enter the BSL-4 itself, the Attending Veterinarian has full independent access, and on behalf of the committee, now enters the lab a minimum of once weekly; from within the lab, the AV now submits (by email or fax) a weekly observation report that specifically addresses all items detailed in the semiannual IACUC inspection form. Six members (scientists, OHS members and veterinarians) of the IACUC have access to the restricted area corridor (current smallpox vaccination required for entry) which serves as a support area for the facility, including animal needs, and tour this support area during semi-annual inspections; these members also

meet with senior PIs working within the BSL-4 suites at that time. While this in no way substitutes for actually going inside the facility, these inspections have identified areas of concern, and also allow a direct discussion with the PI about the protocols being conducted in the BSL-4 area.

In addition to the initiation of weekly inspection reports from the AV, IACUC oversight of the BSL-4 areas has been improved with the installation of video cameras in the BSL-4 suites. The moveable video cameras allow the Attending Veterinarian, ARB Branch Chief and members of the IACUC to view the animal housing and use areas from a remote location at any time. The cameras will also allow semi-annual inspections to be conducted in person by [redacted] or another IACUC designee, and viewed at the same time by members of the IACUC. We are also strongly considering adding an external consultant to our semi-annual inspection team who has been cleared to enter BSL-4 facilities. This would allow two inspectors "on site", and would also provide an unbiased review of the BSL-4 program.

In addition to the weekly reports sent from within the BSL-4 suites, a regular report on the BSL-4 has been added to the agenda of the monthly IACUC meeting. This report is provided by the veterinarians providing support for the animal studies. The veterinarian responsible for providing animal care in the BSL-4 area will enter the facility a minimum of once a week and provide a written report to ARB. These reports will be reviewed at the monthly meeting of the IACUC. All husbandry is now being provided by ARB, which will also facilitate adequate monitoring. In addition, SRP has retained an external IACUC specialist to serve as a consultant and to assist in a comprehensive review of CDC's IACUC structure and function, which will include further addressing BSL-4 area issues.

3. IACUC Structure and Function

3.a. Insufficient oversight regarding IACUC protocol review procedures, post-approval monitoring, semiannual program review procedures and investigation of animal health concerns. Examples include:

RESPONSE:

The CDC has initiated a series of actions to improve the IACUC oversight of animal care and use at the CDC. The IACUC program office will be moved from the Office of the Director, National Center for Infectious Diseases (OD/NCID) to the Centers for Disease Control and Prevention, Office of the Chief Science Officer (CDC/OCSO) and staffing will be increased from the current single position to a total of 4 administrative staff. These will comprise a program manager, an IACUC administrator, support for the GRANITE protocol module, and a secretary. The program manager will be responsible for the overall direction of the program and for compliance with all relevant regulations. This position will work closely with the IACUC and Institutional Official to ensure that CDC's program is functioning optimally. The IACUC administrator will be responsible

for all administrative aspects of protocol submission, review and approval, and for support of the IACUC meetings. One staff member will provide technical support for the GRANITE protocol software, and the secretarial position will provide administrative support for the IACUC office itself. This will provide an oversight structure similar to that for the IRB at CDC. The program office will be responsible for oversight of the animal care and use program at CDC, administrative support to the IACUC, quality assurance and post-approval protocol monitoring. Location of the IACUC Office within that of the Chief Science Officer will significantly increase its visibility at CDC, and will also enhance interaction with the Institutional Official, which will facilitate better regulatory oversight and institutional support.

In addition to the staff outline above, we propose recruiting a quality assurance officer, as recommended by the program review performed by outside consultants last fall. This position would also be responsible for assuring that adequate training was delivered across all aspects of the program. We also plan to establish a position to perform post-approval monitoring of protocols. Both of these positions would be located in the IACUC office.

As previously mentioned, we have engaged an IACUC consultant who will be reviewing all aspects of the current structure and function of CDC's IACUC. We expect to have a significantly enhanced program in place by the time of the next semi-annual inspection at the end of March.

3.a.1. The semiannual assessment reflected semiannual facilities inspection, but no clear record of a semiannual program review.

RESPONSE:

The programmatic section of the semiannual review is currently conducted by reviewing a checklist of important programmatic issues at the IACUC meeting following the semi-annual inspection. Deficiencies are noted, and the report submitted to the Institutional Official together with the findings from the facilities inspection. We plan to significantly augment the entire semi-annual review and follow-up, and will be discussing ways to achieve this with the IACUC consultant mentioned above. Enhancement of the program will be a regular topic at the IACUC meetings.

3.a.2. The GRANITE protocol management system does not track the specific information changed as required by the IACUC in an initial application for animal use. The result is incomplete records and inadequate assurance that work is being done in accordance with the approved protocol.

RESPONSE:

CDC has been using GRANITE for protocol submission for the past two years. One of the strengths of this software package is that is allows direct comparison of all versions of a protocol from the original submission through

final approval and then any amendments subsequently approved. This is a tremendously valuable feature. The following two paragraphs describe how this is accomplished.

To track and compare the changes between a submitted protocol and a previous version, a reviewer may opt to "Compare to a Previous Version" in the navigator window. Also, any changes to a submitted protocol/amendment can be identified and tracked through the "Submission Item Change Report". This GRANITE feature compares the old version to the new and isolates modified areas to print a report. This feature also displays the differences between approved protocols and subsequent amendments.

For a submitted protocol/amendment, all comments/concerns/questions are easily viewed in the "View Review Information" for each submitted version of the protocol. For an approved protocol/amendment, all comments/concerns/questions are available in the "Protocol History" feature through the "View Review Information" for each submitted version of the protocol.

All comments made at each stage of the review process are also documented in GRANITE. Changes requested by the IACUC at the monthly meeting are entered into the system and returned to the investigator to be addressed. Changes made in response to these comments can be tracked as described above.

Once the protocol is approved, we currently rely predominantly on our animal technicians and veterinary staff to assure that the work is being conducted according to the approved protocol. In order to make sure that all staff listed on a protocol know what is in the final version, they all have access to GRANITE on their desktop computer, which allows them to check the protocol at any time. As described above, we plan to establish a position dedicated to post-approval monitoring of protocols.

3.a.3. The description of the approval process for protocols is poor due to the lack of guidelines or policies.

RESPONSE:

The current process of final protocol approval after the IACUC meeting is as follows:

- All changes requested by the IACUC are documented at the meeting. These are generally minor clarifications, such as defining needle length or confirming exact numbers. The clarifications are discussed with the PI at the IACUC meeting, so that the committee is clear about

the investigator's intent. If major changes are required, the protocol is returned to the PI, and the protocol voted on at a later date.

- After the meeting, the IACUC Executive Secretary, who is a non-voting member of the IACUC, enters the required changes into GRANITE and returns the protocol to the investigator, who makes those changes. The amended protocol is returned to the Executive Secretary, who reviews the changes (as described above) and if they conform to the IACUC's request, then approves the protocol. All of these interactions are documented in GRANITE, and the Executive Secretary's final approval is recorded as a separate voting tier.

A charter is being prepared to fully articulate the role, policies and procedures of the IACUC. This charter will also clearly delineate the IACUC approval process and appropriate procedures for modification of protocols. IACUC policy letters are also being developed.

3.a.4. There is no specific 'off protocol' care or management plan specific to chimpanzees that are no longer on study.

RESPONSE:

CDC has had an approved holding protocol for naïve Chimpanzees in place for some time. All chimpanzees not on an active protocol are assigned to the holding protocol. The placement of off-study chimpanzees onto the rhesus holding protocol was a clerical error on the part of the area manager. The inactive animals should rather have been attributed to Chimpanzee Holding Protocol 1260KRACHIC. This protocol was modified in August to include post-experiment chimpanzees for clinical monitoring while on site.

3.a.5. Insufficient number of personnel to ensure animal well-being likely contributed to three incidents involving primate death.

3.a.5.i. Dehydration of two animals attributed to prevention of continuous access to water by dislocation of the lixit from the cage.

RESPONSE:

Water lixits were examined and all found to be loosely affixed were properly adjusted to ensure the animals had continuous access to water. An SOP has been developed and water lixits are routinely checked for proper positioning and patency by animal care staff at a minimum of twice each day and recorded on the daily checklist sheet. The procedure for checking the water lixits requires caretakers to use a clean stainless steel rod to manually deflect the lixit in each occupied cage in order to visually verify the proper positioning and the proper flow of clean water from the lixit. A select number of animals (Aotus, Saimiri, and select macaques) also receive a supplemental fluid bottle containing Pedialyte, affixed to the

front of the cage and changed daily. Area Supervisors also check rooms daily to ensure proper positioning and function of water lixits, among other daily checklist items. Staffing will be adequate to perform all husbandry duties noted at all times.

3.a.5.ii. The procedure-related deaths of non-human primates were investigated by an external review committee. The recommendations of the external review committee had not been fully implemented to prevent future occurrences of using a novel anesthetic regiment at potentially high doses with insufficient number of personnel to monitor the condition of each animal.

RESPONSE:

The procedures cited were subject to both internal and external review, and a number of changes have been made to minimize any similar future incidents. As a matter of clarification, this incident was performed by the Attending Veterinarian for the facility and occurred while using published recommended doses of injectable anesthetic and analgesic combinations; the anesthetic used (Telazol®) was listed in the approved protocol, and the analgesic employed (butorphanol) was added by the AV as a matter of clinical judgment at the time of sample collection, based on the size of the subjects and the sampling protocol (rectal mucosal biopsies through a colposcope). After the deaths occurred, the IACUC conducted an investigation, and consultation with colleagues who had used these agents in combination revealed that the published doses in contemporary laboratory animal formularies were too high for butorphanol. External consultants brought in to review the deaths subsequently agreed with this finding. Thus, if this anesthetic/analgesic combination is used again, future doses will be decreased accordingly. Emergency support supplies and drugs have also been established on each floor of the facility. All future sample collections from animals that require a surgical plane of anesthesia will be performed in the ARB Treatment/Surgery suite with adequate personnel and staffing support.

3.b. The Animal Policy Board (APB) served as an inappropriate oversight body as stated in its internal policies and processes.

3.b.1. IACUC authority is overridden by the APB policies for local animal care and use. Notably, the policy states that the IACUC's task was to implement the APB policy, which conflicts with the federally mandated methodology for program management and oversight.

3.b.2. Directives stated in the APB policy applied at outside institutions trump local IACUC authority and conflict with AWRS, PHS Policy, and the Guide.

3.b.3. APB policy had the APB Chair appointing members to the IACUC instead of the Chief Executive Officer or Institutional Official.

3.b.4. The advisory nature of the APB, as noted in a September 2002 letter to OLAW, was not reflected in APB documents or leadership opinion. True APB function was unclear and may be inappropriate.

RESPONSE to 3.b.i. through 3.b.4.:

The Animal Care and Use Policy describes the overall policies for animal care and use at CDC. As a part of those policies, the Animal Policy Board was intended to function in an advisory capacity to the Institutional Official in order to ensure that there were not wide disparities between the way the three IACUCs at CDC operated, and also to provide a forum for discussion of new developments in animal welfare and in safety aspects of the program. The APB was not intended to dictate policy to the IACUCs. We recognize that the policy document is poorly worded, and we have decided to abolish the APB and constitute an Animal Care and Use Advisory Committee similar to the model used at NIH. The exact composition of this committee will be determined after consultation, but the chairs of CDC's three IACUCs (Atlanta, Morgantown and Ft Collins) will sit on the committee. Once the composition and function of this committee is established, the Animal Care and Use Policy will be amended to reflect this new advisory body. Although the wording of the policy document is unintentionally ambiguous, IACUC members have always been appointed by the Institutional Official.

3.c. Chimpanzee management practices were not acceptable

3.c.1. There was no record of Interagency Animal Models Committee (IAMC) review and approval for any CDC-owned chimpanzee usage.

RESPONSE:

Recent IACUC changes now require all chimpanzee protocols to be reviewed by the Interagency Animal Models Committee (IAMC) prior to use in a research study. All currently active chimpanzee protocols now have IAMC approval.

3.c.2. The practice of 'limit feeding' to prevent chimpanzees from reaching 50 kg in size must not be a strategy for retaining animals for CDC studies. Sound rationale for limit feeding is required.

RESPONSE:

We are concerned that there may have been some miscommunication between the AAALAC site visitors and CDC staff about chimpanzee management practices. We have reviewed our records and interviewed staff, including the principal investigator who has worked with these animals for the past 15

years, and we are confident that "limit feeding" of chimpanzees is not practiced at the CDC. The CDC has a policy of retiring chimpanzees from research when they reach 50kg because current facilities are not appropriate to house animals beyond this weight. Over the past two years, the CDC has retired five chimpanzees to a private chimp sanctuary because they exceeded the 50kg weight determined by the IACUC and the Occupational Health and Safety Office as appropriate maximum weight for safe handling at the CDC. The veterinary staff has also consulted with expert colleagues at other institutions housing chimpanzees in an effort to identify non-weight related "retirement" criteria; unfortunately, no consensus criteria currently exist, thus we are continuing to attempt to identify appropriate benchmarks.

3.c.3. There was no written policy stating that any given chimpanzee may be used on more than two survival procedures. Numerous examples of multiple survival procedures were observed.

RESPONSE:

The reference to two survival procedures in this section requires clarification. We believe that the report was referring to ultrasound directed percutaneous biopsy procedures. Chimpanzees are used for hepatitis research at the CDC and require periodic ultrasound directed percutaneous hepatic biopsy. The current limit established by the IACUC is for no more than three percutaneous hepatic biopsy attempts with an 18 gauge needle on a single chimpanzee per sampling procedure.

3.d. Inadequate or inaccurate recording of animal care, missing anesthetic/analgesic use documentation and incomplete animal medical information were evident in the IACUC approved protocols, facility management records and postoperative records.

RESPONSE:

The management of animal medical records has been problematic. Most of the difficulty arises from an inadequate animal records management system incapable of tracking animals as they move between the three animal facilities, an insufficient number of clinical veterinarians, and too few veterinary technicians and animal caretakers to support the animal research effort. Recently, the CDC hired a new clinical veterinarian and a new ARB Chief. The addition of two veterinarians significantly increased the clinical support for research animals. Clinical veterinarians have been directed to complete all medical records in a timely manner. Additionally, funding has been made available to purchase an animal medical records management system. Significant progress has already been accomplished in the management of existing records. The chimpanzee medical records have been improved substantially to include all documentation for anesthetic and analgesic medications. The records have also been improved to provide all clinical assessments and laboratory test results on each animal in a

timely manner. Medical records have been created for all USDA regulated species. Hiring actions have been initiated and funded to hire additional animal care staff, and applications have been received for review.

3.d.1. Completion of effective therapy regimen for post-procedural pain management was inadequately recorded. Examples:

3.d.1.i. Following a major operative procedure, a squirrel monkey [redacted] was prescribed minimal doses of analgesics in the veterinary plan. The medical record did not record administration of the medication or an explanation of the change from daily dosing for two weeks as required in the veterinary plan to a single week.

RESPONSE:

We would like to clarify that this animal (#2145) was actually housed and cared for at the [redacted] The major operative procedure performed was not a fracture repair, but amputation at the knee. The analgesic buprenorphine was prescribed and administered as indicated in the record. The procedure was performed on 6/27/05. Buprenorphine was administered twice daily from 6/27/05-7/10/05. The plan required twice daily dosing for two weeks, which the animal received and is documented in the file on the treatment sheet; a copy of the treatment sheet can be provided if needed. If we have misinterpreted the issue of concern or if there has been any miscommunication, we will be happy to discuss this issue further at the appeal.

3.d.1.ii. Documentation of medication for anesthesia, analgesia or recovery from percutaneous liver biopsies was missing in the records for two chimpanzees.

RESPONSE:

The management of animal medical records has been problematic. Medical records for Comet and Hunter, in addition to all of the other chimpanzees have been significantly improved over the past six months. Medical records are now prepared using the Subjective, Objective, Assessment and Plan (SOAP) format and all anesthetic and analgesic are appropriately logged into the system. Clinical veterinarians have been directed to complete all animal medical records in a timely manner. A subcommittee was established and a SOP developed to ensure veterinarians and animal health technicians complete all pertinent information in animal medical records. The subcommittee also recommended purchase of the Veterinary Medical Records System to improve records management. The CDC recently made funds available to purchase the system.

3.d.1.iii. Rationale for exceeding the maximum attempts for a percutaneous liver biopsy was not provided in a case where ten attempts were recorded for one chimpanzee. Provision for follow-up monitoring and IACUC consultation for deviation from approved protocol methodology were unclear.

RESPONSE:

It is unfortunate that ultrasound directed percutaneous hepatic biopsy was attempted a total of 10 times on an animal in August, 2004. The IACUC has established a maximum of three ultrasound directed percutaneous hepatic biopsy passes using an 18 gauge needle on an animal per sampling procedure, and a formal policy has been generated. All ARB veterinarians supporting the hepatitis program received additional training from the ARB consulting radiologist. A one-day course was conducted for all ARB veterinarians charged with the responsibility of performing ultrasound directed percutaneous hepatic biopsy. All collections with chimpanzees are performed with an ARB veterinarian present, and the collection of tissues (blood volumes, number of biopsy samples, etc.) are referenced and strictly limited to what is in approved experimental protocols. Additionally, the new record system features a dynamic report in each animal's record that fully documents all sample collections.

3.d.2. Records for chimpanzees, baboons, and macaques [redacted] were incomplete.

RESPONSE:

On 29 August 2005, a comprehensive animal health record system was enacted for all chimpanzee housed at CDC. In this system, all clinical and experimental procedures are fully documented in SOAP format in the individual record maintained for each animal. Included within the SOAP entry for each event is a full accounting of periprocedural provisions, observations and responses, patient monitoring from induction to recovery, and pain management relevant to the procedure and protocol (when applicable). With each SOAP entry, each record now contains fully corroborating documentation for all medications administered for each event, and for patient monitoring during recovery from anesthesia when utilized. The record keeping system enacted for chimpanzees was reviewed in October, and following a positive evaluation, was approved in November for maintaining the health records for all other NHP's housed at CDC. As a starting point, semi-annual physical exams were performed on all NHP's [redacted] campus in December, and those data are now being incorporated into existing animal health records using the new record keeping format.

3.d.3. Managing the medical care plan, case resolution and assessment of animals was difficult due to maintenance of animal care records in two or three different databases or physical locations.

RESPONSE:

The fragmented state of animal health records at CDC has been decreased through enactment of a comprehensive in-house electronic and paper animal health record system, as noted in the response to 3.d.2. In the revised record keeping system, eight distinct sections in NHP records provide for documentation of:

- Master problem sheet and protocol assignment/status (quarantine, holding, on study, etc.)
- Clinical record in SOAP format, with inclusive separate documentation of medications administered and monitoring of anesthetic recovery
- Weight record
- Diagnostic test record (TB tests, blood work, etc.)
- Animal health notifications submitted for LATG and/or veterinary attention
- Physical exam and surgery record, with a summary report maintained as the cover sheet
- Clinical diagnostic summaries and treatment record
- Behavioral record, including behavioral observation and assessment, and a behavioral master problem list

The clinical records for rabbits, ferrets, goats, hamsters and guinea pigs consist of two-or four-section folders, with most of the data captured in the clinical record section. Group records are now maintained for rats and mice.

In the revised record system, each animal health record features a master problem sheet in the front panel of the record folder that provides a chronologic summary of clinically significant events, along with dates of resolution; a similar but separate behavioral master problem list is maintained in the behavioral section of the record. The revised record format also features clinically relevant summary data at the top of every new form created in the record; a dynamic "running" medical history is included within the animal ID section, and documentation of exposure to experimental agents is included in the experimental protocol information section. These summary presentations, in combination with the revised clinical record format, readily facilitate the routine and normal assessment of animals by individuals

requiring health care information, and comprise in one site all information necessary to follow a medical care plan or case resolution.

3.d.4. Veterinary medical information was not routinely accessible to the veterinary care team. Information is divided between researcher's experimental records and animal records maintained by ARB.

RESPONSE:

The Veterinary Medical Records System will provide the opportunity to place medical records in a digital format so they will be available to veterinarians and technicians at all three animal facilities. The system can also be adapted to include pertinent information from investigator records. This system will eliminate the operational void between medical records and investigator records and provide a seamless tool to properly manage research animals.

3.d.5. Animal health records do not exist for any USDA regulated species other than chimpanzees and macaques [redacted]

RESPONSE:

Medical records have been prepared for each species regulated by the Animal Welfare Act. As noted in the response for 3.d.3, individual records have been created for all USDA-regulated species. Additionally, group records have been created for rats and mice to allow for complete documentation of clinical and experimental manipulations, as necessary.

3.d.6. [redacted] there were discrepancies between the controlled drug log and the amount present in the controlled drug storage cabinet. Also, vacutainers partially filled with a clear liquid and labeled buprenorphine were in the cabinet.

RESPONSE:

A review of the ARB controlled substances program was conducted in June 2005. This review resulted in modification of the program at all three animal facilities. Prior to this review, ketamine hydrochloride was accounted for by the full (unopened) bottle only. Bottles of ketamine hydrochloride that had been opened but only partially used were not maintained in the controlled substances perpetual logbook. The new policy mandated tracking of all controlled substances by the milliliter and recording the amounts in a ketamine hydrochloride usage logbook.

It is our belief that while undergoing this operational transition, the findings by the site visitors were correct based on the information provided and most likely resulted because the bottle of Ketamine hydrochloride was logged into this newly formed Ketamine usage log book, and was not logged into the old perpetual inventory of controlled substances log (bulk inventory sheet). In

transitioning, we inadvertently did not log the information on the latter sheet and we believe this accounted for the difference in the amount of drug recorded in the logbook and the amount maintained in the safe.

The finding "The controlled drug log also indicated that 10 bottles of buprenorphine were under lock, but 10 full bottles and 5 vacutainers partially filled with clear liquid and labeled buprenorphine were also in the cabinet is accurate. However, because of a miscommunication on our part, the site visitors were not made aware the shelf in the locked cabinet was labeled "expired drugs, awaiting destruction by the drug control officer".

Several steps have been taken to improve the accountability of the controlled substances program. First, a SOP has been developed to clearly articulate procedures for the maintenance of controlled substances. Secondly, a disinterested officer from the CDC Drug Service office conducts a quarterly inventory of all controlled drugs. Thirdly, training is providing for all personnel authorized to administer controlled drugs in support of the animal care and use program.

3.d.7. The system for drug management did not provide adequate tracking of use required for prevention of abuse or pilferage. Despite an audit revealing discrepancies, the system had not been changed.

RESPONSE:

A new Standard Operating Procedure has been established for the procurement, management, storage and disposition of controlled substances at the CDC. The CDC Drug Service audits the ARB controlled substance program. We have discontinued the practice of accounting for Ketamine hydrochloride at the bottle level to accountability for each milliliter and significantly reduced the number of individuals with access to the controlled drug storage area. This new SOP significantly improved the management of controlled drugs by requiring for the first time that a disinterested officer is responsible for the quarterly inventory of all controlled drugs received by the ARB.

3.e. Certain BSL-4 practices were inconsistent with expectations. For example:

3.e.1. Movement of rodents from bioclean hood to a laminar flow station increased the risk of agent exposure for personnel in event of suit failure.

RESPONSE:

We regret that this comment may have resulted from miscommunication regarding the videotape presentations of the BSL-3 and BSL-4 areas. The incident referenced by the site visitor in this section did not occur in the BSL-4 area, but rather occurred in the BSL-3 area [redacted] an area in which both influenza and monkeypox conduct active research. The movement of

animals in the BSL-3 suites was reviewed in coordination with Occupational Health and Safety and the influenza branch, and practices within the area and related SOP's have been modified so that no cages containing experimental animals are uncovered unless and until positioned inside the BSC within the room.

3.e.2. Transport of small rodent cages (some with wire-bar lids), euthanasia and complete necropsy of animals in multi-purpose areas increased risk of contamination.

RESPONSE:

As noted in 3.e.1 above, the incident referenced by the site visitor in this section did not occur in the BSL-4 area, but rather occurred in the BSL-3 area [redacted] the specific incident videotaped was the culling of animals on several of the approved monkeypox protocols. Procedures conducted and performed in the common corridor area, including the transport of animals from animal rooms to necropsy, have been reviewed with Occupational Health and Safety, and detailed procedures for properly decontaminating the area are in place, as noted in the ARB SOP's.

3.e.3. Housing of both naïve and experimental rodents on the same side of a ventilated rack system under positive pressure increased the risk of agent exposure for personnel in vent of suit failure. Plus, it may have impacted the research data outcomes due to common air flow/exhaust stream.

RESPONSE:

In the BSL-3 area, mixing of naïve and experimental rodents within the same rack has been discontinued; experimental rodents are maintained in microisolator cages within the rooms, which are under negative pressure relative to the hallway and common area; naïve animals are maintained in microisolator cages under positive pressure inside BioClean units.

According to current BSL-4 practices, all rodents –naïve and experimental- are maintained in covered microisolator cages housed in Thoren HEPA filtered units; rodents of different species (i.e., mice and rats) are maintained on different Thoren racks. Each microisolator box on the Thoren racks is maintained under negative pressure relative to the room, and the exhaust air is HEPA filtered. While it is not ideal to house naïve and exposed animals on the same rack, such housing occurs in the BSL-4 suites due to an economy of available space. Specific practices are employed to prevent transfer of agents among cages, and continuous virologic testing has confirmed no unexpected transfer of infectious agents between animals housed in separate microisolator boxes on the same or on different racks, nor contamination of naïve animals during the period of time (> 5 years) this housing practice has been employed.

As part of the quality assurance plan, the BSL-4 will be included in the areas monitored by use of sentinel animals.

4. Husbandry and Sanitation Programs

4.a. Numerous overcrowded cages of rodent and rabbit too large for their cages were observed. The animal care staffing level for the number of animals appeared insufficient.

RESPONSE:

All rodents and rabbits on CDC campuses are currently housed in species-appropriate sized caging, in accordance with standards contained in the Animal Welfare Act (CFR, Title 9, Chapter 1, Subchapter A - Animal Welfare: Part 3 Standards). Physical exams have been performed on all rabbits, ferrets, hamsters and guinea pigs, and current weights were used to determine appropriate housing per animal. All microisolater cages housing mice or rats have been visually inspected, and group housing of these animals is appropriate for the weight and number of animals resident to each group. The current staffing level for ARB is insufficient to meet the growing demands of the CDC. Several hiring actions to increase animal support personnel have been forwarded to human resources for action. Two additional animal caretaker positions have been approved and advertised, and applications to fill those positions have been received and are under review. Both an Office Administrator and a Deputy Branch Chief have been hired. Additionally, Investigators have been advised that animals will only be ordered prior to eminent use. A comprehensive review of animal space usage has been performed to allow for consolidation and economy of space utilization. At the same time, a census has been performed of the resident animal population to identify animals that are listed on active protocols but have remained unutilized for extended periods, resulting in the usage, transfer, or removal of a small number of animals of various species.

4.b. Significant concerns for sanitation practices, to include:

4.b.1. The number of soiled cages awaiting sanitation and additional cages stage for autoclaving indicated the lack of sufficient resources to accomplish required sanitation tasks.

RESPONSE:

Frequent sanitation equipment breakdowns [redacted]he main animal facility [redacted]resulted in the backlog of soiled caging and equipment. Provision of support from the Facilities and Engineering Office has improved with the commencement of contract services. Work orders have been submitted to address the existing sanitation equipment problem and the Facilities and Engineering Office has assigned specific individuals with extensive experience in cage wash repair to support ARB. Outside

consultants from commercial vendors of cage wash materials and equipment have been brought in to assess the nature of equipment failure and to suggest appropriate preventive measures where applicable. This has resulted in a 10-15% decrease in downtime of cage wash equipment, with a concordant decrease in the backlog of dirty caging. The service representative from PRL Pharmacal has been scheduled to hold equipment usage and training classes the second week in January, which will focus on preventive maintenance of equipment, and this should further decrease equipment downtime. During periods of critical backlog of dirty caging, ARB has been authorized to use the cage wash facility [redacted] during times when the [redacted] cage wash is down for repair. These steps should significantly improve and ultimately eliminate the backlog of soiled cages.

4.b.2. Occupational health and safety and animal care risks are posed by the method of equipment sanitation and sterilization [redacted]. Quality assurance mechanisms were not in place to validate adequate disinfection through Vesphene foam prior to transport [redacted] for sanitization. The sanitized cages were loaded back on the sanitized truck (again, lack of validation of sanitization process) and transported [redacted]. Funds for construction of a cage washer [redacted] were withdrawn.

RESPONSE:

A cage wash and autoclave facility has been approved [redacted]. An interim cage wash facility has been approved for installation [redacted] until a permanent cage wash facility can be installed in the animal holding facility [redacted]. Ground was broken in late December for the interim cage wash facility, and should be completed in February 2006. We anticipate the permanent cage wash facility will be completed by September, 2006.

4.b.3. Wooden handle brooms with natural fiber brush cannot provide the level of sanitization required nor can they be sanitized effectively.

RESPONSE:

All wooden handled brooms have been replaced to facilitate more appropriate sanitation of the workspace and related equipment. All wooden handle items were discarded and replaced with sanitizable plastic-handled items as of August 31, 2005.

4.b.4. Use of 70% alcohol for surface disinfection may not be adequate for some microorganisms.

RESPONSE:

Alcohol (70%) is not approved as a surface disinfectant, nor has it been an approved as a sole or primary agent for disinfection according to SOP.

Animal support personnel have been directed to use only approved cleaning agents as specifically noted in the OHS section of approved protocols, which is the source of information posted on the room entry instruction sheet posted outside of each animal room. Alcohol (70%) continues to be used as an adjunct and/or secondary disinfectant for surface cleaning delicate laboratory equipment.

In such cases, the appropriate usage of alcohol (70%) is noted on the room entry instruction sheet posted outside of each animal room. Vesphene, Nolvasan, and Chlorine bleach are approved for use as disinfectants. Vesphene is used in animal rooms and support areas. Nolvasan is used in the treatment rooms and chlorine bleach is used in the primate areas.

4.b.5. The use of bulk tunnel washing for sipper tubes as an alternate to the sipper tube washer had not been verified for effectively sanitizing the sipper tubes.

RESPONSE:

A work order has been submitted to repair the sipper tube unit [redacted] All sipper tubes are placed in a basket and sanitized in the tunnel washer. Sipper tubes are routinely tested for adequate sanitization using swab test kits, and tunnel washer performance is monitored and documented according to SOP; documentation of testing results are maintained in a log by the facility manager, and documentation of tunnel washer performance is maintained by the contract service provider. Failure of a swab kit test and/or documentation of failure of a tunnel washer cycle (inadequate temperature, etc.) result in the machine being taken off line for a service check; during such time, sipper tubes are cleaned and sanitized by hand, with sanitization verified using swab test kits.

4.c. The use of inappropriate agents for insect control without the knowledge of ARB staff or IACUC does not apply as an effective vermin and insect control program.

RESPONSE:

The use of Vesphene to control the insect infestation was practiced by the pest control contractor and not by ARB personnel. ARB personnel reported the inappropriate use of vesphene to their supervisors and this practice was immediately terminated. A meeting was held with representatives from the pest control contractor and the CDC project officer to ensure this practice never occurs again.

5. Occupational Health and Safety Program (OHSP)

5.a. Determination of personnel participation in an animal oriented OHSP should be based on the criteria given in the Guide, instead of the current policy of those who had "substantial animal contact."

RESPONSE:

As part of the IACUC review process, safety professionals from the Office of Health and Safety review every animal protocol that is submitted. This review includes a risk assessment that takes into account not only the containment of infectious organisms, but the pre-existing health status and safety of both the animal care staff and the animals within the facility.

To further safeguard their health and well-being, all animal care personnel are entered into a formal medical surveillance program at the time of hire. Laboratory managers and supervisors are responsible for enrolling scientific staff involved with laboratory animals before initiation of their own protocols. Maintenance and other staff who may only need to occasionally enter animal areas are also enrolled into a modified medical surveillance program based upon the risks of their specific responsibilities. Cardkey access to the animal facility requires proof of medical clearance.

All personnel entering medical surveillance programs are medically cleared prior to animal area entry by onsite, occupational health clinics administered by the CDC Office of Health and Safety. These clinics are staffed by physicians and support personnel who are familiar with the activities and risks of the animal care work performed. The Office of Health and Safety utilizes an automated immunization and medical surveillance tracking system to monitor compliance with medical tests, screenings and immunizations. This system also sends automatic notifications to workers and their supervisors when additional interventions or annual updates are required.

Components of the program include:

- Initial Animal Resources Branch Fitness for Duty exam
  - Height, weight, B/P, Pulse
  - Vision/ color perception
  - Baseline serum
  - Hepatitis C titer
  - Td booster if >10yrs. since last immunized
  - MMR immunization or titer
  - Positive varicella history or titer
  - Hepatitis A, B, Rabies immunizations or Hepatitis B and/or Rabies titers as indicated
  - 2 step TB skin test
  - Respiratory clearance and fit testing and training
  - Audiogram
  - Physical exam performed by NP or PA for Fitness for Duty

- Evaluation of position description, risk assessment, and physical abilities (ability to lift 40lbs above the head)

- Annual renewal exam
  - Baseline serum
  - Hepatitis C titer
  - Rabies titer
  - TB skin testing (done every 6 months)
  - Respiratory clearance and fit testing and training
  - Audiogram

5.b. Use of non-HEPA filtered vacuum cleaners in animal use environments presented an occupational health risk.

RESPONSE:

All non-HEPA vacuums have been removed from the animal areas. Specifically, the non-HEPA vacuum previously located in the ABSL-3 suite [redacted] has been removed.

5.c. Use of engineering controls for containment of infectious agents must be the primary method of personnel protection, rather than total reliance on personal protective equipment, especially during cage changes.

RESPONSE:

In areas containing infected animals, biosafety cabinets will be used for the changing of small animal cages. Where biosafety cabinets are not available, cage changing stations or other appropriate primary containment devices will be purchased and used for cage changing. OHS staff will work with the IACUC and veterinary support staff to identify these locations and acquire the equipment. OHS has identified candidate portable changing stations from Nuaire and has forwarded the specs [redacted] for consideration.

5.d. The creation of a conference room adjacent to the autoclave [redacted] *created a hazardous and hot service area for operation.*

RESPONSE:

Work orders to repair the flooring and improve the ventilation and lighting in the area in question [redacted] have been submitted to CDC FEO. A temporary cage wash facility is slated to be on-site by February 2006. A permanent cage wash and autoclave facility is scheduled to go online in September, 2006.