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[Sent by express mail and email]

May 30, 2008

Attention: Dr Robert Gibbens

USDA/APHIS/AC
2150 Centre Ave.

Building B, Mailstop 3W11
Fort Collins, CO 80526-8117

RE: Inspection Report, date April 15, 2008; University of California, Customer
ID: 9199

Dear Dr. Gibbens:

The University of California, San Francisco ("UCSF") hereby appeals the citations listed in the Inspection Report dated April 15, 2008 (the "Report" a copy of which is attached for your convenience). For the reasons explained below, we believe that many of the citations either lack factual support or are misunderstandings. We request that these citations be removed.

Item I—Institutional Animal Care and Use Committee

Background:

The Report notes a deficiency in the IACUC involvement regarding case V000335, a 6yr old animal with recurrent inappetance and sustained weight loss at least partially due to iatrogenic masticatory myositis/fibrosis. Specifically and in pertinent part the Report, states:

"(d) IACUC review of activities involving animals. 1) In order to approve proposed activities or proposed significant changes in ongoing activities, the IACUC shall conduct a review of those components of the activities related to the care and use of animals and determine that the proposed activities are in accordance with this subchapter unless acceptable justification for a departure is presented in writing; (i) Procedures involving animals will avoid or minimize discomfort, distress, and pain to the animal

The salient portion of the USDA report describes:

'Animal Number V000335 was assigned to a food restriction protocol. Records for this animal showed aggressive implant/skin margin cleaning, differing antibiotics, and supplemental nutrition. The weight of the animal near the start of the study was 9.65 kgs (March 2007) and the weight of the animal at the time of this inspection was 7.12 kgs. (25% weight loss). The veterinarian removed this animal from the food restriction portion of the protocol at 10-15% of weight loss but allowed primary investigator of the research study to continue to manage the diet of the animal. This animal was also being treated for a chronic infection of the soft tissue of the skull caused by a surgical procedure.'

"The description in the record of this animal indicated a malodor coming from the area of the cranial implants. It was also noted in the records problem with the temporomandibular joint. It was later determined by the investigator that there was a possible fibrosis of the muscles surrounding the mandible. This animal continued working for food supplements in the restraint chair for the purpose of collecting protocol related data,"

"The records of both animals indicate a distress and discomfort.... There were no records of IACUC involvement/intervention or review of these animals for distress and discomfort...."

Issues

1. Regarding *"the veterinarian removed animal from the food restriction portion of the protocol at 10-15% of weight."*

Animal V000335 began food restrictive study on 04/26/06 at 6.6 kgs and ended on 8/13/07 at 8.74kgs. So he actually did well. The overall weight gain was in excess of 30%. At no point during that time period had weight loss neither reached 10%, nor required veterinary intervention. The food restriction portion ceased, per protocol on 8/13/07 for surgery. The protocol states *"After full recovery from surgery (at least one week post-surgery) animals will be employed for chronic neurophysiological and microinjection experiments."* Therefore at the time of inspection the animal was on a non-food restricted short term terminal study.

2. Regarding food rationing having remained at the discretion of the primary investigator despite marked weight loss.

To clarify this point, the dietary management remained under the veterinarian's direction at all times other than that noted in issue 1 immediately

During February 2008 a reduced appetite and selective feeding was noted. Eventually it was determined to be caused by a muscular-skeletal problem limiting mastication. Other medical conditions may have contributed. The diagnosis as stated in the medical records entry from 3/31/08 includes:

3/31/08 "Poor appetite and body condition, moderately poor skin turgor. EENT: Markedly reduced range of motion of the temporomandibular joint and potential fibrosis due to inflammatory disorder or infection, no evidence of arthritis elsewhere in body.....Assessment- Temporomandibular joint disease possibly due to fibrosis induced at surgery and/or soft tissue inflammation from physical trauma or infection Plan-Discuss with PI and provide all solids via slurry....."

This diagnosis was later confirmed, and more precisely characterized as fibrosis of the masseter muscle, by the principle investigator. In retrospect, this condition may have contributed to the unexplained weight loss following implantation given muscular fibrosis is the result of myositis.

It should also be noted that this finding preceded the inspection by a matter of days and that this animal was on a non-food restricted short term terminal study at the time of inspection.

5. Regarding the claim that the IACUC in concert with the veterinarian allowed animals continued use as research subject and for the sole purpose of collecting protocol related data.

This procedure permitted the treatment of this animal (prescribed in the medical record entry of 3/31/08 above). Chair restraint was also required for proper treatment and care of the implant. Lastly, it was deemed by the veterinarian and behaviorist to be beneficial for wellbeing by providing stimulation and socialization. The claim is wrong.

6. Regarding the concern of an IACUC failure to involve itself in the review of animal care, regarding research animal V000335 care, distress and discomfort.

IACUC minutes reveal that on Nov 6, 2007 this animal's weight loss was carefully reviewed by the IACUC, to-wit:

"The weight charts of ...[includes this animal]...were approved. It was noted that an animal in the ...lab with greater than expected weight loss had been assessed by LARC veterinarians who were unable to determine the specific cause despite performing physical exam and multiple tests....."

above. Records of what food was provided were maintained and the clinical veterinarian and veterinary support staff kept a careful watch over these amounts. The problem was not that the animal lacked enough food (please note that researcher involvement was under the control of the veterinarian(s)). The problem was that the animal did not eat enough of the provided food to maintain its weight.

Following surgery on 8/13/07 post-surgical complications, including acute weight loss, warranted the animal remain off study pending veterinary clearance. After two months the animal had regained good health, though weight loss was sustained. The animal was cleared for non-food restrictive study, and a variation in food rationing was prescribed to conform to the needs of the animal and the research project. Here are relevant entries in the medical records to show the progression in recovery and approval:

9/17/07 "BAR, reported to readily consume pasta, nutella and V8. Peanut shells and grapes present on cage bottom. Appears to eaten two burger balls but neither soaked nor plain biscuits. A – Improved mentation and appetite."

10/4/07 "...Biscuit consumption has increased.....Implant margins are healing appropriately. Mentation is excellent..."

10/9/07 "Consumed 18 of 20 biscuits provided over weekend. Reported to have weight decrease despite good appetite A-Stable....."

10/17/07 " BAR, normal posture and attitude. No signs of discomfort. A- Stable P-Allow lab to work animal using an alternative feeding regime (uneaten food removed from cage in AM and animal fed full ration in PM). Animal is to receive full ... ration each day"

The modified feeding regime consisted of having the PI supply food as animal tasked, then provide the animal with full ration upon return to the cage. Husbandry staff would then remove, quantify, and document all unconsumed food items remaining in the cage the following morning.

3. Regarding specific references to infections. UCSF requests that all reference to aggressive margin cleaning, malodor be removed from the paragraph. It is inflammatory and does not directly relate to the USDA inspector's cited concern.

4. The Report fails to clearly depict the diagnosis, contribution, and management of the fibrosis affecting the jaw.

IACUC minutes for January 15, 2008 discuss this animal again, as follows:

“One animal [this animal] is below baseline and was removed from study in July. Vets have observed the animal and noted that the body condition is good [Note weight was in 8.5 kg range], weight is stabilized, and appetite is healthy. Veterinarians may consider approving lowering of the baseline weight.”

At the same meeting the IACUC reviewed a weight record for animal V000335 and information from the research group was furnished to the IACUC at that time, to-wit:

“As evident in the chart, the [animal’s] weight has been under the 90% baseline mark through-out the duration of this quarter. LARC veterinarians are fully aware of this and have kept him off food restriction for this reason....”

Here is a summary of this animals weights for May 2007 to April 2008.

Time	High (kg)	Low (kg)
May 2007	9.81	9.0
June 2007	9.66	9.2
July 2007	9.7	8.9
August 2007	9.0	8.65
September 2007	8.65	8.2
October 2007	8.1	7.8
November 2007	8.7	8.0
December 2007	8.5	8.15
January 2008	8.5	7.9
February 2008	8.0	7.66
March 2008	8.05	7.15
April 2008	7.24	6.8

USDA inspector's concerns are that:

“The IACUC should have in concert with the veterinarian determined if these two animals were distressed and/or discomforted and made efforts to correct their conditions prior to allowing the continuation of their use as research subjects....[t]here were no records of IACUC involvement/intervention or review of these animals for distress and discomfort...”

UCSF believes that had the inspector seen these IACUC minutes they would have satisfied his well-founded concerns as clearly there are several records

of IACUC involvement and intervention. UCSF did not point this out at the inspection. However UCSF did not understand that the USDA inspector viewed this as a deficiency during the inspection. Thus UCSF was denied the opportunity to satisfy the inspector's concerns. Had UCSF realized that was an inspector's concern UCSF would have provided these minutes for review.

The facts show the IACUC was very involved in this matter and was in consultation with LARC veterinarians. The weight loss had only recently become severe. As recently as March 17, 2008 the animals weight was over 8.0 kg.

Again, UCSF veterinarian staff closely monitored the condition of this animal. Given the extensive and voluminous number of medical health entries, it was one of the most observed animals currently on a research protocol. IACUC reviewed the case. It was not an animal lacking in veterinary care or IACUC oversight. As written the citation undermines the veterinarians in their provision of clinical care and invites the IACUC to render second opinions on clinical cases.

Requested action:

- i. UCSF requests that this citation be removed in its entirety. A full review of the facts demonstrates the IACUC's deep involvement in this animal's care and close consultation with veterinarians.
- ii. If USDA disagrees and the citation is not entirely removed, UCSF requests the citation be rewritten to correct and/or clarify the above six issues to accurately reflect this case report.
- iii. UCSF also specifically requests that the citation state that the IACUC reviewed the animal's condition on at least two occasions and that the IACUC's review is reflected in the IACUC minutes.

Item II—Institutional Animal Care and Use Committee

Background:

The Report notes a deficiency in the IACUC involvement regarding animal MMU 35184, an 8 year old animal with a pre-existing dermatopathy (identified upon arrival in 2005), diagnosed as atopic dermatitis 6 months prior to the inspection. Specifically and in pertinent part the Report, states:

"(d) IACUC review of activities involving animals. 1) In order to approve proposed activities or proposed significant changes in ongoing activities, the IACUC shall conduct a review of those components of the activities related to the care and use of animals and determine that the proposed activities are in accordance with this subchapter unless acceptable justification for a departure is presented in writing; (i) Procedures involving animals will avoid or minimize discomfort, distress, and pain to the animals;"

The Report list animal MMU 35184 as an "animal identified during this inspection described as atopic and severely pruritic."

Of the more than 133 animal health records entries, the pruritis has never been classified as severe. Representative veterinarian entries regarding severity of pruritis include:

10/31/07	<i>"mild to moderate scratching"</i>
11/05/07	<i>"no scratching seen"</i>
12/07/07	<i>"no scratching seen"</i>
12/10/07	<i>"pruritis is moderate and extensive"</i>
12/14/07	<i>"animal is not as pruritic in our presence as previously noted"</i>
12/17/07	<i>"no obvious signs of pruritis"</i>
12/21/07	<i>"reported to be mildly pruritic"</i>
12/26/07	<i>"pruritis and rash of varying severity"</i>
01/01/08	<i>"pruritis continued since prior exam"</i>
01/07/08	<i>"displays odd mock scratching...itches various areas"</i>
01/10/08	<i>"still pruritic"</i>
01/16/08	<i>"partially responsive pruritis to steroid tx"</i>
01/22/08	<i>"gradual resolution"</i>
02/01/08	<i>"little evidence of pruritis"</i>
02/07/08	<i>"atopy nearly in complete remission"</i>
02/15/08	<i>"not scratching"</i>
02/22/08	<i>"evidence of pruritis is minimal however still present"</i>
03/13/08	<i>"not scratching"</i>
03/20/08	<i>"rash not visible nor is evidence of pruritis"</i>
04/03/08	<i>"no obvious signs of severe pruritis"</i>
04/07/08	<i>"Slightly pruritic, waxing and waning atopy"</i>

The animal received extensive care upon being diagnosed atopic and the condition remains under control. All care and treatment is by UCSF clinical veterinarians who have no relationship to the research group. In the opinion of the clinical veterinarians attending this case, it was neither severe nor significant enough for the IACUC to be apprised of the animal's condition. UCSF veterinarians provided good care and exercised excellent professional judgment in treating this animal's condition.

For USDA veterinarians to now provide a second veterinarian medical opinion based solely on review of medical record entries oversteps the intention of the animal welfare regulations framework, where researcher animals are cared for by the institution's veterinarians.

Likewise to suggest that the IACUC must engage in the degree of review proposed for this particular animal leads to undermining the veterinarians authority to exercise considered professional veterinary medical judgment regarding the significance of any particular condition.

The clinical veterinarian(s) have experience with primates and would apprise the IACUC of significant clinical cases. In their professional opinions this case did not rise to that level and was being medically managed. IACUC general programmatic oversight would only arise when the condition became clinically significant. In fact there are entries in the medical records whereby the treating veterinarian(s) deemed the condition as not serious or significant and that the animal could remain on study.

10/31/07 *"condition is mild- animal can stay on study"*
12/27/07 *"slight scratching, thickened skin, may stay on study"*

UCSF emphasizes this is not a situation where veterinary care was absent, nor did the case lack a diagnosis, nor was the veterinary care below the standard of care for the condition. Adequate and effective veterinary care was being rendered.

UCSF believes that either UCSF failed to make the situation clear to the inspector, or the inspector misunderstood the case. Nevertheless, UCSF does not believe that it this animal warrants inclusion as part of any citation.

Action requested:

- i. UCSF requests that this citation be entirely removed along with Item I.
- ii. If USDA disagrees about item I and the citation is not entirely removed, UCSF requests the citation be rewritten as follows:
 - a. Remove the following sentence from the Report: *"Animal Number MMU 35184 is another animal identified during this inspection described atopic and severely pruritic."*

b. Modify the subsequent paragraph which currently reads, in pertinent part as follows so as to remove all reference to the atopic animal (suggested changes in italics):

"The records of *both* animals indicate a distress and discomfort while continued use for the collection of data for research. Animals that have chronic infections directly related to the surgical procedures associated with the study and a severe weight loss of undetermined cause, *or as in the case of the other animal, atopic and severely pruritic indicates animals* that may be discomforted....The IACUC should have in concert with the veterinarian determined if *these two* animals were distressed and/or discomforted and made efforts to correct *their* conditions prior to allowing the continuance of *their* use as research subjects.....there were no records of IACUC involvement/intervention or review of these animals for distress and discomfort and it is their responsibility to ensure the avoidance of pain, distress and discomfort as per this section of the regulations."

Item III— Defective caging.

Background:

The Report noted a deficiency in the design and condition of certain non-human primate cages. Specifically and in pertinent part the Report, states:

"Structure: construction. Housing facilities for nonhuman primates must be designed and constructed so that they are structurally sound for the species of nonhuman primates housed in them. They must be kept in good repair, and they must protect the animals from injury, contain the animals securely, and restrict other animals from entering."

"Animal MMU 35184 has a history of getting extremities caught in different areas of the primary enclosure. There were 4 instances of this animal having extremities trapped in the last 3 years. The most recent occurrence was in February 2008 when the left arm or [of] the animal was trapped in a small area on the front corner of the primary enclosure. There has been no adjustment or alteration to the animal enclosure at the time of this inspection to prevent recurrence."

MMU 35184 [actually the number is 35183] is housed in a primary enclosure designed and furnished by Primate Products Inc. These are the same cages USDA cited as being improperly designed and constructed in its August 7, 2006 report for a locking mechanism inadequacy.

At that time, UCSF contacted the CEO of the company and informed him of USDA's concerns. The CEO came to the UCSF campus, examined the cages and provided a letter indicating that the cages were in good condition and repair. (A copy of that letter is attached and was previously furnished to USDA).

Regarding the August 7, 2006 concern, UCSF subsequently retrofitted the cages and applied a safety chain to address even the slightest possibility that these squeeze mechanism might present a hazard to monkeys manipulating them.

Now, UCSF is told that the cages are improperly "*designed and constructed*" because a very active animal finds a way to manipulate the cage until he gets his hand stuck. Yes, the animal got his extremities stuck on rare occasions as indicated. The report does not state that he ever suffered any injury as a result of possessing Houdini-like abilities.

The cited regulatory standard is that the primary enclosure must "*protect the animals from injury, contain the animals securely, and restrict other animals from entering.*"

No facts support a claim that the animal was injured, was not secured or that another animal entered. For that reason alone, the citation exceeds the regulatory guidance and is improper.

Subsequent to the most recent inspection UCSF has retrofitted the cages again and this is even more retrofitting than was done last time.

Primate Products Inc. cages are used in many other institutions. Primate Products Inc. is one of the largest most well respected primate cage manufacturers in the world. Primate Products, Inc.'s website says that it is "the world's leading developer and distributor of enrichment devices, handling equipment, quality housing systems, and many other services designed specifically for nonhuman primates."

<http://www.primateproducts.com/home.php>.

UCSF does not have the exact number, but we suspect that there are thousands of these cages in existence. UCSF suspects that other institutions use these exact cages with similar monkeys and experience similar events that are the subject of the 2006 and 2008 citations. UCSF is unaware of any other institution receiving a citation related to Primate Products Inc cages. UCSF also is unaware of any other institution that has gone so far as to have the CEO of the company come inspect that cages and deem them in good repair. UCSF would like to know if there are any other institutions with similar citations so that it can approach the company with this information.

UCSF is using what it believes are state-of-the-art primate cages that were in perfect working order. If USDA cites UCSF for the design of these cages, then in fairness it should cite every other facility that also uses these cages.

Given the August 2006 report and now the April 25, 2008, it seems that the USDA inspector does not approve of Primate Products Inc. cage systems. If that is true UCSF will either junk the Primate Products Inc cages and not

purchase these caging systems in the future (which the company states are in perfect condition for these monkeys), retrofit them even more extensively, or look for another alternative.

That said, if USDA had a concern about these cages, August 2006 was the appropriate time to express it not 2 years later. The message that UCSF is getting is that no matter what steps it takes to modify the properly designed Primate Products Inc cages something else will come-up.

UCSF invites, encourages and asks that the USDA take a close look at this cage system here and elsewhere (such as the large primate centers in the country which have them). After the review, UCSF hopes that USDA gives its list of concerns in one final document to Primate Products Inc. and all of their cage users.

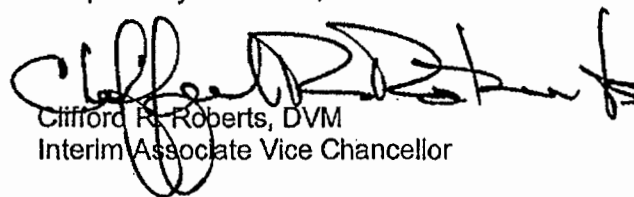
Barring that UCSF asks that the USDA consider this a matter of fairness. It is being singled-out for using cages as designed and in the manner intended. It remedied concerns expressed in 2006. It now receives new concerns in 2008 on the same cages and with the same animal.

Action requested: For all of these reasons UCSF does not believe that at this moment in time the citation is appropriate and respectfully requests that it be removed. UCSF then asks that USDA work with it to remedy any and all concerns about UCSF's use of this properly designed caging system.

Dr Gibbens, UCSF wants to note that it is making every possible effort to run an excellent animal care program. In good faith we do not believe there was significant deficiency on this particular matter. We appreciate your patience in considering this appeal.

UCSF looks forward to working with your office on this and all matters relating to animal care.

Respectfully submitted,



Clifford R. Roberts, DVM
Interim Associate Vice Chancellor

Cc
Eugene Washington, EVC