**IACUC Training Exercise #3 – 2021 (What to Do About a Possibly Reportable Matter)**

The following exercise is a continuation of exercises #1-2021 and #2-2021, and may be useful in stimulating discussion regarding compliance with PHS Policy and VA Handbook 1200.07. To facilitate discussion, pages 1 and 2 of the exercise may be distributed to the IACUC members prior to a meeting. After a few minutes of discussion about the exercise during the meeting, the remainder of the exercise may be distributed to provide ideas for the committee’s consideration.

Recall: Matt Johnson, the lead technician for Dr. Carol Wang, an investigator at the Hometown VA Medical Facility, was cleaning and treating a surgical incision of an anesthetized cat with a newly developed agent designed to improve healing where the wound is subject to movement stress. Because the procedure is short, the cat had been anesthetized with an intramuscular (i.m.) injection of a mixture of ketamine and midazolam, which typically allowed plenty of time for the entire procedure and was less stressful on the cat than mask induction with isoflurane would be. The procedure took a little longer than usual, and Matt noticed a slight increase in the cat’s respiratory rate, suggesting the cat was in a lighter plane of anesthesia, which needed to be corrected. He asked his assistant, Jerry Kim (an undergrad student volunteering in the lab to gain some research experience), to administer a small supplemental dose of the ketamine/midazolam mixture. Jerry saw that there was not enough of the mixture left, and found that the bottle of midazolam they had used to make it up was empty, so he got out a new bottle, carefully made up more of the mixture, drew up the volume that Matt had said to give, administered it i.m., and recorded the dose on the surgical notes. Matt finished the procedure without incident, and the cat recovered uneventfully. A week later, Matt was cleaning the lab and noticed that several bottles of midazolam with the same lot number, including the one that Jerry had opened during the surgery on January 14, had actually expired three days earlier, on January 11. Matt used the required procedure to dispose of the expired midazolam so it could not mistakenly be used again. Matt provided a written report about this for the IACUC. The Chair had appointed the Attending Veterinarian to investigate, and put the matter on the agenda for the next IACUC meeting. The IACUC discussed whether the matter was reportable, and if so, what should be reported.

Next: Then, the Non-Scientific Member asked, “Is there anything else we need to know about this, besides what Matt wrote?” That’s when the Chair called on the Attending Veterinarian to tell the committee what she had learned in her investigation, and she said,

“I expected this to be a pretty straight-forward situation when I started, but it turned out that there are a few more things to consider. When I talked with Matt, he told me that it had surprised him when the anesthetic level seemed to be getting lighter, but he also recalled that the procedure had taken more time than usual that day, so he assumed that the cat just needed a supplement. But then we took a look at the surgical record, and it showed that the time when he asked Jerry to give the supplement was still well within the period when the original dose of ketamine-midazolam should have been effective. Matt also recalled that the typically calm cat had been agitated by a new resident in the cat colony, which may have been a factor in why a supplemental dose was needed

So then I asked about how Dr. Wang’s personnel keep track of expiration dates on the drugs, and Matt could only say that they’ve never run into this problem before, because they usually only order what they are going to use soon, so everything is used up well before it expires, and there’s no need to pay much attention to the specific dates on the vials. Jerry mentioned that he had never thought to look at the expiration dates. I talked with Dr. Wang, who was surprised that the vials of midazolam had expired, and wondered whether the latest order had been filled with vials much closer to expiration than usual.

A couple of other things came up when I asked to look at the protocol. First, Matt did not have a copy handy, and Jerry said he had never seen it, as he was just observing and doing whatever Matt asked him to do. It’s not good that they did not have a reference copy handy. I eventually got a copy of the approved protocol from Anne Marie, and noticed a second problem, which is that the protocol explicitly describes giving only one dose of ketamine/midazolam without allowing any flexibility to supplement as needed to maintain an appropriate plane of anesthesia. Even without that flexibility written into the approved protocol, I could of course always authorize a supplementary dose, but Matt and Jerry gave the supplement without approval in the protocol and without consulting with me.”

**For IACUC discussion (Question 1 of 1): Is any of this new information from the Attending Veterinarian relevant to the IACUC’s decisions about (1) what corrective actions are needed, and (2) whether anything needs to be reported to ORO and OLAW?**

1. Corrective actions

Although disposing of the vials of expired midazolam will clearly prevent their contents from being administered to any more animals, the Attending Veterinarian’s observations suggest that some better mechanism(s) should be established in Dr. Wang’s lab to keep track of expiration dates. These could include things like the following:

* Whoever receives delivery of new orders should circle the expiration date on each vial, to notice what it is, and make it easier for others to find.
* Whoever draws up any of the contents of the vial should note the expiration date along with the dose in the veterinary medical records for the animal.
* As part of orientation for each new person involved in the work with animals, it should be mentioned that attention to expiration dates is part of everyone’s responsibility.
* The frequency of post-approval monitoring of Dr. Wang’s laboratory will be increased for the next six months or longer to ensure the above practices are implemented.
* The IACUC will give extra attention to expiration dates during semiannual inspections and inform the investigator if any drugs are within three months of the expiration date.

A reference copy of the most recently approved version of each protocol that is actively being followed in the lab should be kept available in some convenient location in the lab.

The protocol should be modified to address the options available to maintain the appropriate level of anesthesia for the procedures being performed. These could include administration of supplementary ketamine/midazolam, administration of isoflurane by nose cone, or (if additional anesthetic would invalidate the research) withdrawal of the animal from the study.

1. Reportability

According to OLAW FAQ F.5, the administration of an expired drug “is not consistent with acceptable veterinary practice or adequate veterinary care”, so “anesthesia and analgesia agents should not be used beyond their expiration date”. According to Matt’s description, the use of the expired midazolam appears not to have negatively impacted animal welfare, so it would be up to the IACUC to determine whether this represents serious or continuing noncompliance with PHS Policy.

The Attending Veterinarian found that the supplementary dose of ketamine/midazolam was given without IACUC approval in the protocol, and without consultation with the veterinarian, which made it a “failure to adhere to IACUC-approved protocols” (one of OLAW’s examples of reportable situations).