ANIMAL TRACKS
A newsletter for the Duke research community
http://vetmed.duhs.duke.edu

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PHARMACEUTICAL GRADE COMPOUNDS

Recent updated from the NIH and publication of the new National Research Council document The Guide for the Care & use of Laboratory Animals have made it abundantly clear that all research institutions must re-evaluate the use of non-pharmaceutical grade compounds in research animals. For most Duke research activity, the new positions don’t have much impact as all Duke animal care & use previously required pharmaceutical grade use for anesthesia, analgesia, and euthanasia; certain very specific exceptions (e.g., Avertin).

⇒ Researchers can review several sources for relevant information regarding the new regulatory positions.
For example: USDA’s Policy #3: Veterinary Care
⇒ NIH / OLAW Non-Pharmaceutical Use
⇒ USDA/NIH/ AAALAC Webinar
⇒ Transcript of Webinar: Non-Pharmaceutical Use
⇒ NRC’s 8th Edition of The Guide (Page 31)

So, how does all of this regulatory language shake out for the individual researcher at Duke? Well, the Duke IACUC has set in place a Policy on Non-Pharmaceutical Use. It could be helpful to review the policy as the Committee has attempted to craft a position which is applicable, flexible, and accommodating. At least as accommodating as one can be within the context of new federal regulatory requirements. The Committee will also consider ‘Exemptions to The Guide’ when the policy prevents researchers from achieving their research goals. ‘Exemptions’ may be approved, but that approval must be based upon scientific necessity for need. Cost, convenience, or ‘we’ve always done it this way before’ is not an allowable justification by the feds.

Other questions (and answers) are listed below which may be of value to those considering the use of non-pharmaceutical meds. The Q&A’s are based upon a Webinar given by representatives of the Office of Laboratory Animal Welfare at NIH (OLAW), the United States Dept. of Agriculture (USDA), and the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC), held on March 1, 2012 (hyperlinked above).

For a set of specific FAQ’s regarding non-pharm use, see Page 2.

Wishing you a safe and productive research month!

IT IS TIME FOR AAALAC TO VISIT DUKE AGAIN

Once every three years, we are visited by the Site Team from the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC). Our next scheduled visit will occur during the fall of 2012. As we all prepare for the next visitation, you might present these questions at your next laboratory meeting. All members of your research team should be able to answer ‘YES’ to each of these questions. If not, please provide guidance on the specific item, or call the OAWA (668.6720) and Bill Wade can visit with your laboratory staff and review AAALAC expectations.

1. Do we have copies of all of our approved protocols (and amendments) where our research staff can review them?
2. Are all of the research staff familiar with the protocol procedures they are working on?
3. Are we using only analgesics / anesthetics that are in our approved protocol?
4. Are our controlled substance licenses current and our controlled substance logs up to date?
5. Are we following the HUMANE ENDPOINTS listed in our protocol?
6. Can all of the surfaces in our animal use areas be adequately sanitized?
7. Do all of our staff understand (and can they explain) Duke’s veterinary care reporting system? Does our research staff know how to contact a Duke veterinarian after hours if needed?
8. Are our animals observed at least daily, including weekends and holidays?
9. Have our research staff completed the required animal training? Safety training?
10. Are all of our cages of animals labeled with CURRENT PROTOCOL cage cards and have the required PI information?

The animal program would like to help your lab be a shining star during the 2012 AAALAC accreditation site visit!

Upcoming Dates & Deadlines

May 3 Amendment meeting
May 7 New Protocol deadline
May 17 Amendment meeting
May 24 New Protocol meeting

Deadlines are 5 PM on the date listed!
FAQ’S on NON-PHARMACEUTICAL USE

FAQ #1: Are investigators required to use a compounding pharmacy when it is necessary to use a specific mixture of experimental drugs, chemicals or other formulations?

OLAW, USDA and AAALAC consider the compounding of investigational agents or the customized manipulation by dilution or addition of vehicles to pharmaceutical-grade substances for administration to animals as necessary and acceptable scientific activities carried out by researchers. However, these activities should be described in the animal study and reviewed and approved by the IACUC.

FAQ #2: May investigators use a commercial compounding pharmacy to prepare specific mixtures of experimental drugs?

Yes. There may be circumstances where the customized manipulation of an FDA approved drug by a licensed pharmacist is needed to meet the needs of a research study. Examples include mixing two injectable drugs into a specialized formulation, preparing a paste from crushed tablets or adding flavoring to a drug. FDA states that for compounding by a pharmacy or veterinarian to be legal, it cannot be from bulk or raw active ingredients, although FDA does under specific circumstances allow this practice.

FAQ #3: May investigators prepare the specific mixture themselves in the laboratory?

Yes. However, these activities should be described in the animal study and reviewed and approved by the IACUC.

FAQ #4: When it is necessary to add a vehicle or diluent to a chemical or substance that will be administered to an animal, is it required to use a pharmaceutical grade material?

It depends on the route of administration and the need to maintain sterility. The focal concern is that the product does not injure the animals and is appropriate for the science. Professional judgment should be used in making this determination. For oral administration, the vehicle or diluent should be food grade. For injections such as intramuscular, intraperitoneal, or subcutaneous, the diluent or vehicle should be sterile and physiologic.

FAQ #5: Does the requirement distinguish between the use of non-pharmaceutical-grade substances for medical / veterinary and research use?

The general philosophy concerning the selection and use of compounds for clinical or therapeutic applications and for research applications in laboratory animals is the same. The Guide recognizes that pharmaceutical-grade compounds afford the subjects protection against toxic or unwanted side effects potentially minimizing important variables in scientific studies. Compounds used in veterinary and human clinical applications are routinely available in a pharmaceutical-grade and should be used whenever possible. However, scientific studies may require the use of compounds that are not available in pharmaceutical-grade, or that may only be available in a pharmaceutical-grade that is legitimately deemed unacceptable for particular scientific reasons. In these cases, with appropriate IACUC oversight, non-pharmaceutical-grade compounds may be acceptable when prepared and maintained using sound pharmaceutical practices.

FAQ #6: Does the requirement force us to use a more expensive substance that does not confer any additional benefits over a less expensive substance?

The question as stated does not reference any quality factors of the substance other than expense. All oversight bodies support the prudent use of scientific resources. If both products have acceptable efficacy, there is no need to spend any more money than is necessary.

FAQ #7: Is the dilution of a drug such as Ketamine with saline for use in the mouse considered compounding?

No, it is considered an adulteration of the original product, but one that is necessary to ensure that the appropriate dosage is administered. As long as proper sterile technique and a sterile diluent are used, there should be no issues of concern for the IACUC.

FAQ #8: Can the IACUC approve the use of tribromoethanol (also known as Avertin)?

Avertin is the trade name for the injectable anesthetic agent 2,2,2-tribromoethanol. Avertin was once manufactured as a pharmaceutical-grade drug. It is no longer available commercially. The preparation and use of tribromoethanol for anesthesia needs to be scientifically necessary, appropriately justified and approved by the IACUC, taking into consideration the side effects, stability, storage requirements and other considerations associated with the preparation of this agent. There are multiple reports in the literature of physiologic harm to animals including ileus, adhesions and mortality from the use of tribromoethanol. AAALAC has no objections to the use of Avertin in IACUC-approved protocols. However, OLAW would advise IACUCs to critically evaluate the proposed use of tribromoethanol and the consideration of alternative methods that avoid or minimize discomfort, distress and pain. Furthermore, OLAW has recently learned of journals turning down studies for publication that described use of tribromoethanol.
FAQ #9: Is it necessary to use USP or Grade A (Medical) CO2 to euthanize rodents?
Either USP Grade A (medical) or Grade B (industrial) carbon dioxide may be considered acceptable as they each provide a minimum purity for carbon dioxide of 99.0%. Carbon dioxide should be supplied in compressed gas in cylinders. The use of dry ice is unacceptable according to AVMA Euthanasia Guidelines (PDF).

FAQ #10: Can euthanasia solution be diluted and used as an anesthetic for survival surgery? Can euthanasia be used as an anesthetic for non-survival surgery?
No. Typically these solutions are not sterile and contain drugs other than anesthetic agents that could harm or kill the animals even if diluted. A euthanasia solution may not be used as an anesthetic for survival or non-survival procedures. OLAW in concert with USDA agree that a procedure may be performed as a part of euthanasia. And this would be limited to terminal perfusion or exsanguination. In both cases, death is an immediate outcome of the procedure.

FAQ #11: Is it OK to use non-sterile euthanasia solution for euthanasia?
Yes. This is consistent with the adequate veterinary care under the Animal Welfare Act, Paragraph 2143, Subparagraph (a)(3)(A) and the Animal Welfare Regulations 9 CFR Chapter 1, Paragraph 2.33, Subparagraph (a), (b)(2) and (4) in which a humane death is achieved.

FAQ #12: Can non-pharmaceutical-grade pentobarbital be used for euthanasia?
It can be used if scientifically justified and satisfies the paragraphs from the Act and the Regulations previously cited.

FAQ #13: Does the NIH non-pharmaceutical-grade substance policy apply to aquatic species?
Yes. The guidance is applicable to aquatic species because the composition of the drug either -- both the purity, solubility and toxicity -- are just as relevant in the case of aquatic species as well as other animals. And special attention needs to be given to drug concentrations in the volume of water in which the animal is placed.

FAQ #14: OLAW FAQ F4 states, "...the IACUC may establish acceptable scientific criteria for use of these agents within the institution, rather than on a case-by-case basis." How might this be used?
This is similar to an IACUC approving a standard operating procedure for a surgical procedure. If the IACUC bases its approval on a scientifically justified reason -- for example, non-availability or greater purity of product and has clear guidelines on issues like reconstitution, handling, storage -- then use of a non-pharmaceutical-grade compound may be considered for an institution-wide approval.

USDA Seeks Comments on the Use of Humane Endpoints and Methods in Animal Testing of Biological Products
The U.S. Department of Agriculture (USDA) Center for Veterinary Biologics (CVB) is seeking comments on Draft Notice 465, which provides proposed guidance on the use of humane endpoints and methods in animal testing of biological products, including specific guidance regarding humane endpoints for the rabies challenge test. The draft guidance also strongly encourages the use of anesthesia for intracerebral inoculation of mice during rabies vaccine testing. Comments on the draft guidance document are due on or before April 23. For more information, visit the USDA website.

NIH ‘Just in Time’ Submission Process Is Changing
The National Institutes of Health (NIH) has announced new policies regarding Just in Time (JIT) submissions. Certain NIH programs and award mechanisms use JIT procedures to enable specific elements of a grant application to be submitted later in the application process, when the application is still under consideration for funding. IACUC approval certifications are among the most common JIT submissions. To reduce application confusion and to minimize requests from NIH staff for JIT submissions, NIH is revising its business processes so applicants will have better information on when JIT submissions are required, and to require electronic submission of JIT information through the eRA Commons (NIH Research Administration homepage) as of April 20, 2012. Full details about the JIT changes are provided in a recent notice from the Office of the Director (NOT-OD-12-101).

What is AAALAC?
AAALAC International is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs. AAALAC stands for the “Association for Assessment and Accreditation of Laboratory Animal Care.” More than 770 companies, universities, hospitals, government agencies and other research institutions in 29 countries have earned AAALAC accreditation, demonstrating their commitment to responsible animal care and use. Duke volunteers to participate in AAALAC’s program of independent assessment of our care & use activities.

For more information, visit the AAALAC website at http://www.aaalac.org
PROCEDURE FOR HANDLING FIRE ALARM ACTIVATION DURING ANESTHETIZED ANIMAL PROCEDURES

PURPOSE: The purpose of this policy is to provide instruction and further clarification with respect to proper procedure during fire alarms and drills. This resolution will protect human life, but will also satisfy the IACUC with respect to animal life.

SCOPE: This procedure should only be followed when the fire alarm is activated during an anesthetized animal research procedure. Research procedures on deceased animals or other animal components are not affected by this policy and those involved are REQUIRED TO LEAVE THE AREA IMMEDIATELY UPON FIRE ALARM ACTIVATION.

SCHEDULED FIRE DRILLS: The OESO Fire Safety Office will post notices of a scheduled fire drill at least 48 hours in advance stating the date and window of time the drill will occur. If an unavoidable conflict arises, the research personnel must notify the OESO Fire Safety office immediately. Our main office phone number will be posted on the notice. If no prior notification is given, the drill will be held, and ALL OCCUPANTS ARE REQUIRED TO EXIT THE BUILDING IMMEDIATELY!

FIRE ALARM ACTIVATIONS:

⇒ In every surgical lab, there will be a poster permanently displayed in a visible location which lists a building contact person, an alternate contact person, and their mobile phone numbers. The designated contact persons for fire alarm evacuations will be determined by the department(s) upon the receipt of this policy. Alternates will also be determined. A list of contact persons and their cell phone numbers will be distributed to all animal procedural areas.

⇒ If the fire alarm is activated, the research personnel shall first check the areas for signs for smoke, fire, toxins or other dangers. ONLY if they do not see any immediate signs of smoke, fire, or other hazards, they will immediately contact the department designated contact person in the building and state that they are remaining in the laboratory because they are performing an animal procedure on an anesthetized animal. If they decide to evacuate, they shall still notify the building contact of this as well. This ensures proper accountability.

⇒ If the research personnel and designee are remaining in the lab, the laboratory designee (if applicable) will continue to serve as a lookout person for signs for smoke, fire, or other hazards, and in charge of communications with the building contact person. If no others persons are in the lab to serve as a laboratory designee, the research personnel must watch for signs of changing conditions to the best of his/her ability.

⇒ The building contact person will notify responding units of the person(s) remaining in the laboratory and their exact location.

⇒ The building contact person will notify the research personnel or his/her designee immediately if conditions deteriorate and evacuation is necessary.

⇒ If evacuation is necessary, the research personnel and his/her designee will then take steps to safely and quickly euthanize the animal (e.g. perform a bilateral thoracotomy while anesthetized), if conditions allow, and evacuate the building immediately.

⇒ If the research personnel are alone when conducting the procedure, the research personnel shall notify the building contact person that the procedure is complete. Any alarms after this point will require prompt evacuation from the building for all occupants.

DEA ANNOUNCES INCREASE IN CONTROLLED SUBSTANCE LICENSE FEES

In a memo sent to controlled substance licensees on March 12, 2012, the U.S. Drug Enforcement Agency announced an increase in licensure fees.

The fee for a controlled substance license has been increased from $184.00 to $244.00.

For more information on controlled substance management when working with animals at Duke, see the Controlled Substance Use & Management Procedures on the Duke Animal Program Website.
**TIPS FOR SURVIVING AN AAALAC SITE VISIT**

Our next AAALAC site visit is fast approaching so we have compiled a list of key areas you can prepare your lab for beforehand. The 2012 site visit will occur in October 2012. During the site visit AAALAC representatives will visit the animal facilities and several of the research labs where animal procedures occur. While we try to give advance notice to labs they wish to visit, often they will make impromptu requests during the inspections. So below are some common topics and issues that have arisen during previous site visits.

**Know your protocols:** The most important thing you and your staff can do to prepare for a site visit or any other kind of inspection is to review and understand what has been approved in the animal protocols. If you discover that changes need to be made you will need to submit a modification. Site visitors will talk to you and your staff about the procedures you perform and they will review your protocols to ensure congruency.

**Ensure personnel are listed on the protocol and have access to the most recent versions:** Since research personnel and students rotate in and out of labs frequently it can often be difficult to keep the paperwork updated. It is very important that all personnel working with animals are listed on the protocols under which they are working and that they have the ability to look at those protocols whenever needed.

**Personnel Protection Equipment (PPE):** Follow signage for PPE on doors of animal rooms.

**Maintaining surgical records:** While detailed animal health records may not be required for the species you work with, it is very important that you are keeping some record of surgical procedures on specific animals or groups of animals. These records should reflect what procedures the animals have undergone and verification that they received the appropriate pre- and post-operative treatment, including analgesia.

**Proper aseptic technique:** It is crucial to apply the appropriate aseptic technique for each procedure.

**Gas vaporizer certification:** Anesthesia vaporizers must be validated according to the manufacturer’s recommendations or annually. DLAR can assist with identifying a vendor to certify your machine (estimated cost of $50/machine).

**Labeled materials:** All materials (such as disinfectants in spray bottles, etc.) must be properly labeled, to include the name of the product and the expiration date of the mixture.

**F-Air Canisters:** Weigh F-Air canisters and record weight before the first use; weight after each anesthetic session and record weight; discard after a weight change of 50 grams. F-Air canisters should be resting on the side, not standing on end.

**Expired materials:** Any substance, material or device that goes in or on an animal as part of a survival procedure must be within its expiration date. Any substance used for anesthesia, analgesia, or treatment as part of a non-survival procedure must be within its expiration date.

**Controlled substances:** Controlled substances must have corresponding log sheets that have been completed with all required information; and the substances must be secured behind 2 locks. Review the Controlled Substance Procedures for more details. If you are unsure about how to dispose of expired drugs or substances please contact OAWA (668-6720).

**Signage:** Know and understand what cage markers indicate and how to respond (such as: Attention Sick Animal, Clinical, Separated, and Overcrowded). Room signs should be printed out and laminated for posting. If you have questions, please contact DLAR (684-3885).

**Special diet storage:** If you are storing a nonstandard animal diet or food treat in your lab, assure there is proper signage, and the diet is stored in conditions based on the manufacturer recommendations. Food must be stored in air tight containers and labeled with the name, manufacture date and/or open date, and the expiration date. If the food item is a common human foodstuff, it must be labeled “not for human consumption”. 

**Needles:** Please do not recap needles. Needles and sharps should be placed directly into the sharps container.

**Safety:** Common safety issues found in labs include unrestrained gas cylinders, failing to replace covers on eyewash stations and conducting work in uncertified chemical fume hoods or biosafety cabinets. If you see any of these issues in the ARP housing facilities, please report it to the ARP building supervisor or care staff.

**Emergency Vet Care:** Know and understand how to contact a DLAR veterinarian for animal health support or emergencies. There is a veterinarian on-call 24 hours a day. The Emergency Vet pager number is 970.9410. Please make sure that this information is prominently displayed in the lab and that all staff is aware of this service. The OAWA has laminated signs available with this information, so please contact us.

**THE KEY!** Just relax and be proud of the work you do in your lab. If you are doing the things listed above and aware of the activities in your lab, there is no reason you can’t be open and excited to discuss your work and animal use with the site visitors.
RESEARCH ANIMAL COORDINATORS AVAILABLE TO ASSIST RESEARCH WITH COMPLIANCE AND TRAINING

In the fall of 2010 the Duke Animal Care and Use Program (ACUP) initiated the Research Animal Coordinator Certification (RACC) program. Twenty-Two students graduated from the first session and are certified by the Duke ACUP as Research Animal Coordinators. After completion of an extensive, focused, nine month program they are well versed in matters of protocol compliance. Listed below are current RACCs by department.

Penny Ferry-Leeper: Ophthalmology  
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Elizabeth Masko: Urology  
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Tomasa Barrientos-De Renshaw: Pharmacology-Cancer Biology  
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Kristina Riebe: DHVI  
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Hilary Bouton-Verville: DHVI  
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Paul Anderson: Steadman Nutrition Center  
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Barbara Theriot: Medicine—Pulmonary  
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David Snyder: Surgery  
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Kelly Barton: Pediatrics-Hematology/Oncology  
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Simone Degan: Chemistry/Radiation Oncology  
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Marybeth Groelle: Ophthalmology  
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Ching-ju Chen: DHVI  
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Mason Webb: Ophthalmology  
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Mark Starr: Medicine—Oncology  
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Jui-Chih Chang: Pathology  
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Melissa Weston: Medicine-Nephrology  
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Katherine Harley: Neurobiology  
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Jennifer Baltzegar: Neurobiology  
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Thomas Rude: Medicine-Infectious Disease  
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Anna Floyd-Avarette: Cancer Biology  
Anna.floyd@duke.edu

George Pitoc: Surgery  
george.pitoc@duke.edu

Erin Potts-Kant: Medicine-Pulmonary  
potts013@mc.duke.edu

The IACUC encourages you to contact these individuals for assistance with protocol Development and compliance, training, preparation for IACUC site visits, OESO or Employee Health questions, etc. RACC Graduates are ambassadors for the animal care and use program and indispensable keepers of knowledge and experience in Biomedical research.

If you have a lab staff member who is interested in participating in the course, Please contact Bill Wade @ 668.6722 or w.wade@duke.edu