BUPRPRENORHINE SR-LAB  
(Compounded Pharmaceuticals)

Buprenorphine produces excellent analgesia in many species, and is especially good for mitigation of pain associated with perioperative procedures, fractures, tissue inflammation, tissue necrosis, and trauma resulting from wounds. It can also serve as an effective foundation in multi-modal analgesia/anesthesia regimens. Thus, it is one of the most widely used opioid analgesics in veterinary clinical practices.

Approximately one month ago, the US Drug Enforcement Agency decided to apply a provision of the Controlled Substance Regulations requiring a prescription for each purchased bottle of compounded pharmaceuticals such as Buprenorphine SR-LAB. Further complicating the situation is that the only registration that is authorized prescription writing for animals is a special form of registration known as a 'veterinary practitioner.'

After consultation with the state and federal agencies, we have received ‘veterinary practitioner’ DEA registration. In a nutshell, the process for obtaining compounded pharmaceuticals such as Buprenorphine SR-LAB is as follows: When the IACUC approves the use of compounded pharmaceutics (such as Buprenorphine SR-LAB), send an email to IACUC@duke.edu requesting a prescription for the purchase of the compounded pharmaceutic.

OAWA will work with you and the pharmacist at the supplier to assure you can obtain the necessary quantities of the compounded products needed for prevention of pain or distress in research animals.

For more details, see the Procedure Plan for Buprenorphine Use in Rodents.

Attached to the end of this Animal Tracks is an information sheet regarding Buprenorphine SR-LAB use in rodents. The main advantage is required administration every 3 days rather than up to 3 times a day with the standard product.

Wishing you a successful research month,
Additional Red Flags
In Doing Alternative Searches
(for potentially painful procedures)

Do your searches have any of these attributes? If so … you will likely be asked for a re-do or clarification.

⇒ The search was completed at the last minute. Searching can be time consuming, so last minute searches may be incomplete.
⇒ Only 1 database was searched. There is an increased bias if only 1 database is searched! For example, PubMed and OVID Medline are basically the same database!
⇒ Terms are only for painful aspects. The search should also include terms for distressful aspects.
⇒ The term “alternative” is the only term combined with the procedure term(s). Searches should also include terms for actual alternatives.
⇒ Keywords listed are not relevant to protocol. Each search should be unique. Be careful about copying and pasting a search from an old protocol.
⇒ Keywords and concepts are linked in an incorrect manner. Have you used the Boolean operators AND, OR, & NOT correctly? (Hint: OR for synonyms; AND between concepts; and NOT with care)
⇒ Search doesn’t cover an adequate time period (5-10 years). An appropriate time period will vary with topic and is a judgment call.
⇒ Found zero results. Most commonly this is because of poor keywords and/or poor use of Boolean operators.
⇒ No word variation. All good alternative searches include: synonyms, truncation, subject terms, and generic and trade names of drug

For more information, see the AWIC presentation: http://awic.nal.usda.gov/workshops/workshop-materials-pdf264-mb or contact the Duke Medical Center Library via their web page.

ENGAGING THE 4 R’S
AND MANAGING THE COST OF RESEARCH

Ed Note: This edition of Animal Tracks initiates a new column which is yet unnamed, but will be presented by those individuals who have been certified as a Research Animal Coordinator at Duke. This RAC Recommendation is provided by Zareen Kapadia (kapad002@duke.edu) from Bioengineering, who observed rapidly increasing per diem charges for animal holding. An internal lab assessment and partnering process within the laboratory resulted in enhanced responsible use of animal resources, refined animal use plans, reduction in the overall numbers of animals, and a significant cost savings. Zareen shares their lab’s success with engaging three of the four R’s of research.

Over 1 year ago I noticed that the monthly mouse charges from DLAR were skyrocketing. Our large lab had many new members added to mouse protocols and their collective increase in animals numbers and the fees for supporting the large increase in animals numbers was not sustainable. To reign in spending we instituted a Animal Review Committee (ARC) within the laboratory. Our ARC is made up of 5 members (one PI, one Research Scientist, 2 senior Graduate Students and the Lab Manager). Animal spending instantly was cut in half the first month and went down by 70% by the 3rd month.

Your lab can easily set up an Animal Review Committee to save money, plan smarter experiments, and save animal lives. All experimental plans must be approved by committee before mouse purchase is allowed. The researcher must first submit a request form outlining experimental purpose and objective, animal number, strain, cost/mouse, fund code, housing location and a breakdown of experimental groups. There is an expected results section and finally, an acknowledgement of requirements for compliance.

A deadline is given for submission of the form. The ARC has 3 days to review and ask questions. The lab manager reviews finances. The applicant has until the 3rd day to answer all questions or revise experiment following suggestions. ARC decision/approval is given by the ARC on the end of the 4th day. In our case by 5pm Friday to allow for ordering of mice by Monday afternoon.

We’ve also set-up a few guidelines and forms to help our researchers meet the goals of resource management and cost containment. I have giving the OAWA copies of these documents, so you can obtain them by emailing IACUC@DUKE.EDU

We’ve fine-tuned our process over the past year. I encourage you to use our method as a guide and revise it to fit your needs. Then watch your spending decrease!

QUIZ QUESTION OF THE MONTH

Question: Whose responsibility is it to assure:
♦ All cages are properly docked in racks?
♦ Animals have water?
♦ Security latches are fully engaged?
Duke Animal Care and Use Program
Training Opportunities

The Office of Animal Welfare Assurance (OAWA) and the Division of Laboratory Animal Resources (DLAR), support of the Duke Animal Care and Use Program (ACUP), by providing training for principle investigators and research staff who conduct work with animal models.

Some of the training opportunities available are as follows:

Monthly Brown Bag Seminars – provides continuing education for the Duke research community through topical and timely seminars. AALAS CE credit approved and also meets the requirement for the Duke IACUC annual CE policy.

OESO on-line training – Animal Handlers Parts I, II & III are required for all new research staff listed on an animal model protocol.

AALAS Learning Library – The Duke ACUP/OAWA maintains 2,000 accounts with this on-line training resource available through the American Association for Laboratory Animal Science. There are 144 courses currently available. Open to all research and animal care staff.

Animal Tracks – A monthly publication from the OAWA that contains new and pertinent information on animal care and use, research methodologies and regulatory updates.

Individual and lab training – OAWA and DLAR staff are available to provide individual and lab staff training on a variety of subjects and procedures. To include handling and restraint, euthanasia, injection and withdrawal techniques, aseptic surgery procedures, consultation on anesthesia equipment, etc.

Contact Bill Wade @ 668.6722; w.wade@duke.edu or Michelle Calkins @ 681.1831; michelle.calkins@duke.edu for training assistance.

CAN YOU SPOT THE CORRECT PLACEMENT?

Ever think you’ll be through with taking tests? Truth is you are never through taking tests, it is just that some tests are the things you do every day, and in some cases, the test we take may have a direct impact upon animal well-being and/or distress.

For example, those of our community that take animal cages from racks and then replace them in the racks after the experiment or cage change – well, every time you place a cage back on the rack … it is a test. If properly done, you passed the test. But if not correctly placed back on the rack, you failed the test and the animal could be injured! Or if not caught, your test failure could cause the death of an animal. Let’s see how good you are at taking the Cage & Rack Test!

Question 1: Of the three cage seating positions shown above (A, B, & C), which one(s) are correct, and which one(s) are wrong?

Question 2: Identify at least one item in each photograph that tells you the cage is properly seated or improperly seated.

Answers on Page 5.

Hey, folks! Please ensure that all caging and equipment are free of defective components before using it!

If faulty equipment is identified DO NOT USE IT! Please place a note on the item indicating it is defective so that the DLAR staff can remove it or repair it!

Remember! I am the most important part of your research resources! Successful research outcomes depend upon keeping me happy and at home! It’s a team effort, you know. NO BUSTED CAGES!

QUIZ QUESTION OF THE MONTH

Answer: The protocol PI is ultimately responsible for all activities approved under their protocol!
Thank Research

If you take medicine to treat allergies • your dog doesn’t have fleas • your grandmother has a new hip • you’ve taken medicine to stop an ache • you’ve never had the measles • you’ve never breathed with the help of an iron lung • you don’t know what bubonic plague is • you control your diabetes with insulin • you take vitamins • your dad has recovered from a heart attack • your great aunt survived breast cancer • your cat doesn’t have feline leukemia • your grandpa has had bypass surgery • your friend has had a stem cell transplant • you’ve had a broken bone repaired • you don’t have ulcers • you’ve had an operation and you slept through the whole thing • you feel great today!!!!

Celebrating the people, the process and the promise

STATES UNITED FOR BIOMEDICAL RESEARCH

www.statesforbiomed.org
Photo A is correctly seated. You can tell that by the absence of any red dot on the side latch, and the absence of any other devices (such as an air supply) on the cage front.

Photo B is NOT correctly seated. You can tell that by the presence of the red air supply port on the lid of the cage.

Photo C is NOT correctly seated. You can tell that by the presence of a red button on the cage latch located on the right side of the cage.

### POLICY CHANGES
**(IN THE LAST FEW MONTHS)**

**Animal Transport into Human Patient Care Areas for Utilization of Diagnostic and Treatment Facilities for Duke IACUC-approved Animal Research:** The main change is the addition of an Animal Transport Manager who will serve as the laboratory ATM for the animal transport and use activity.

**IACUC Review and Approval Practices (Amendments to Approved Protocols):** Now removal of personnel is considered an administrative action, no more minor amendments. YEA! Less Forms to Submit!!!

**Covered Species:** This policy was updated to include actions for feeding live prey in cases where the animals require live feed and will reject any dead or synthetic feeds—an issue of welfare for the prey and the predator.

**Use of the DLAR Holding Protocol:** This policy was clarified as to when the holding protocol should be used in non-compliance or adverse event situations… conclusion, it should be used, not always but sometimes. Give it a read for more information.

**Conducting IACUC Business in the Event of an Emergency:** February 26th, 2015—snow storm and the campus shut down. This was the first test of the animal program disaster plan, and it showed us we needed a few tweaks. Got to keep research approved and moving forward … even during disasters! Need I say more?

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**THE EYES HAVE IT!**

Did you know that skilled observation of the eyes of your animals can give you a very good idea on how they are coping? Why is that important? Because GOOD ANIMAL WELFARE is defined as ‘The ability of the animal to cope with the conditions under which it is living.’ So, good coping means good welfare. And good welfare means stable research foundations, and stable research foundations mean reliable research data! Therefore—good welfare equals good research.

In an article titled: **Using the Mouse Grimace Scale to reevaluate the efficacy of postoperative analgesics in laboratory mice**; (JAALAS 2102), the authors noted that the Mouse Grimace Scale (MGS), “a facial-expression-based pain coding system adapted directly from scales used in nonverbal human populations,” was a “reliable, highly accurate measure of spontaneous pain of moderate duration, and therefore is particularly useful in the quantification of postoperative pain.” The charts below (not from this publication) could be used to help assess the measure of coping being accomplished by our research animals.

<Note: if your animals are not coping well, contact a DLAR veterinarian for ideas and assistance in methods or methodologies to improve the animal’s coping behavior>
Assessment of Sterility in Fluid Bags Maintained for Chronic Use

According to an article by Matthews and Taylor in JAALAS (Sep 2011), multi-use fluid bags present a real but highly variable risk of contamination. The authors assessed the sterility of multiple-use fluid bags in the laboratory setting for a maximum of 60 days. Bags were manipulated to mimic infrequent and frequent use. Bacterial cultures of fluid and bag wall and assays for endotoxin and ATP activity were negative at all time points through 30 days. Two fluid samples yielded bacterial growth at 60 days, although all other tests were negative. The authors suggested that fluid bags used chronically could be maintained in a sterile condition for a maximum of 30 days.

While 30 days seems a reasonable period of time for a multi-use fluid bag, poor aseptic technique could cause contamination in as few as two or three uses and the incorporation of other pharmaceuticals could further interfere with assurance of sterile product.

At present, the Duke animal program does not have a day limit on open bag use, but the program does recognize that many factors must be considered—such as frequency of administration, sanitation of the port surface, aseptic technique used by the laboratory staff, storage conditions of the bag between uses, and visual observation of the fluid product. Obviously, a bag containing floating colonies would not be good nor would a bag first opened in 1978 and stored in a dusty closet until the present.

Recent IACUC visits have noted a intent to economize and keep fluids for extended periods. The IACUC encourages prior planning and good septic practice to minimize the potential impact on research and the well-being of the research animals. To help minimize confusion, always write an ‘opened on’ date on the bag, and consider disposing on fluids that hang around longer than 30 days, or limit the use of older fluids to non-living purposes

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. The 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.

⇒ If evacuation is necessary, the research personnel and 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 fire alarm is activated, 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 is alone when the alarm sounds: If no other persons are in the lab to serve as a laboratory designee, the research personnel staying with the animal must watch for signs of changing conditions to the best of his/her ability. The individual should page the DLAR veterinarian (919.970.9410) and/or the DLAR vet tech (919.812.6943). Any alarms after the initial alarm will require prompt evacuation from the building for all occupants.
Description

Buprenorphine SR™ Lab is a patented injectable, sustained-release polymer system designed to release buprenorphine over a 72-hour period and available by prescription only.

Key Features of Buprenorphine SR™ Lab

- Provides sustained release delivery of buprenorphine in a fully biodegradable liquid polymer matrix
- Provides therapeutic blood levels of analgesia for perioperative and postoperative use (based on published studies)
- Formulation can be injected subcutaneously through needles as small as 23 gauge.

How Supplied and Storage

- Following quality control and stability studies it has been determined that the Buprenorphine SR LAB formulation does not require refrigeration.
- Upon receipt of your Buprenorphine SR LAB vial, it can now be stored at room temperature and will retain its stability through the labeled expiry date.

FAQ’s Regarding Optimal Administration

What are the recommended dose rates for various species? *

Laboratory Rats*: 1.0 – 1.2 mg/kg [In one 72-hour SC injection]  
Laboratory Mice*: 0.5 – 1.0 mg/kg [In one 72-hour SC injection]

* Please be aware that while this novel Buprenorphine SR Lab formulation has been developed specifically for use in some laboratory species, skin reactions may occur in select strains of mice and rats. If so, we recommend that you discontinue use of the Buprenorphine SR Lab.

Should the Buprenorphine be stored and administered at room temperature for use?

Yes, the Buprenorphine SR Lab can be stored, drawn up and injected at room temperature. It has also been determined that using a slow injection technique, decreases animal discomfort (i.e. stinging) during administration.

PLEASE NOTE: While the Buprenorphine SR LAB formulation no longer requires refrigeration, our standard Buprenorphine HCI SR formulations (available in 1 mg/ml, 3 mg/ml, 10 mg/ml concentrations STILL REQUIRE REFRIGERATION.

Are there any other helpful injection guidelines I should follow?

Some helpful guidelines are:

1. While the formulation can be injected through needles as small as 23 gauge, it is recommended that a larger needle (16 gauge to 18 gauge) be used to draw-up the Buprenorphine SR Lab from its vial. This makes syringe loading easier and minimizes loss in handling.
2. Once the required volume has been loaded into your injection syringe, simply remove/replace the larger needle with the desired smaller-gauge needle before administration.
3. Follow recommended US National Institutes of Health guidelines for subcutaneous injections in mice:
   - Restrain the mouse by the scruff method. Use your thumb and forefinger to make a tent of skin over the scruff.
   - Prep the area with 70% ethanol.
   - Insert the needle, bevel up, at the base of the tent. The needle should be inserted parallel to the skin and should be directed toward the posterior of the animal.
   - Aspirate to ensure proper placement and inject the material.

What is the shelf life for Buprenorphine SR?

As ZooPharm is a compounding pharmacy, expiry dates for lots will vary. Typically vials of Buprenorphine will expire 10-12 months from the date of purchase. To find expiry date of the specific lot you will receive, ask our staff when placing your order.

Disclaimer: The information is intended for use by veterinary professionals only and is made available on the express condition that no liability, expressed or implied, is accepted by the authors for the accuracy, content, or use thereof.

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1. Foley PL; Liang H; Crichlow AR Evaluation of a sustained release formulation of buprenorphine for analgesia in rats. JAALAS Vol 50, No 2, March 2011, 198–204

2. Catbagan DL; Quimby JM; Mama KR; Rychel JK; Mich PM Comparison of the efficacy and adverse effects of sustained-release buprenorphine hydrochloride following subcutaneous administration and buprenorphine hydrochloride following oral transmucosal administration in cats undergoing ovariohysterectomy. AJVR, Vol 72, No. 4, April 2011, 461-466