Institutional Animal Care and Use Committee (IACUC)

Policy on Veterinary Verification and Consultation

Date of IACUC Approval: November 4, 2016 Last Updated: January 10, 2020

I. Purpose: The Institutional Animal Care and Use Committee (IACUC) developed this policy to allow certain significant changes to be pre-approved by the IACUC and verified by a Brown University veterinarian, in accordance with the Office of Laboratory Animal Welfare (OLAW) guidance on Significant Changes to Animal Activities NOT-OD-14-126. The goal of this policy is to support the use of performance standards and professional judgment to reduce regulatory burden.

II. Significant Changes allowable with Veterinary Verification & Consultation (VVC)

The following specific significant changes to an IACUC-approved protocol may be processed through VVC, and without full committee or designated member review:

a) Changes to anesthesia, analgesia, or sedation to referenced* drugs and dosages for a given species; examples may include

- A change in dosage, route, frequency or duration within acceptable veterinary parameters;
- Switching from one analgesic, anesthetic, or sedative agent to another; or
- Changing the dosage, timing or route of an experimental substance if the change will not increase the potential for animal pain or distress.

b) Changes to experimental substances, including a change in test compound, dose, or route of administration, as long as the change does not result in a change in study objectives or greater pain, distress, or degree of invasiveness. Note that the addition of a non-pharmaceutical grade drug, or a change from a pharmaceutical grade to a non-pharmaceutical grade drug will *only* be authorized under this mechanism when relevant criteria are addressed and with appropriate justification (see Appendix B).

c) Changes to euthanasia to any method approved in the current AVMA Guidelines for the Euthanasia of Animals, as long as the new method is permitted under Brown IACUC policies. Note that protocol personnel must be adequately trained in the use of the new method of euthanasia under the stipulations of the IACUC-approved Training and Education policy.

d) Changes to duration, frequency, type, or number of approved procedures performed on an animal, as long as the change does not result in greater pain, distress, or degree of invasiveness. The assigned veterinarian may use his/her discretion to authorize minor procedural changes providing in the judgment of the VVC veterinarian the change will not unduly impact animal welfare (i.e., lessens or involves equivalent pain, acute or chronic stress, distress or effects upon animal welfare) and is consistent with current standards of veterinary practice or specifically addressed in IACUC policy. Common examples include:

- Changes related to blood collection (e.g., frequency, volume, vessel of access)
- Revision of sample collection intervals or total samples collected.
- Addition of a non-invasive sampling method.
- Additional perimortem tissue collection or tissue collection from a new organ system or anatomical site when the animal is under terminal anesthesia.
- Substitution of one accepted biopsy method for another for tissue or DNA analysis.
- Altering the duration or interval between procedures (e.g., lengthening an imaging episode or the time between episodes).
- Changing an identification means.
- Adding or altering behavioral testing methods providing they do not involve unrelieved pain or distress.
- Increases or enhancements in enrichment
- Programs of post-anesthetic care that are enhanced above IACUC-approved minimums.

e) Changes to an approved procedure that decrease pain or distress. The assigned veterinarian may use his/her discretion when evaluating such changes and may require IACUC review of the protocol.

f) Change in stock, strain or genetic modification, unless the new stock, strain, or modification results in abnormalities that require special support.

g) Change in animal source (animal procurement)

III. VVC Process at Brown University

The Principal Investigator (PI) must indicate at the time of VVC submission how the proposed changes qualify for VVC and include under which criteria (II. a-g) the amendment qualifies. It is critical that the desired change(s) be well-defined and clearly articulated by the PI. Significant changes that do not qualify for VVC under this policy must be submitted as a substantive amendment to an existing IACUC-approved protocol for review.

ARPP staff will pre-review the submission and verify that the changes meet the criteria for VVC. The ARPP will then consult with a veterinarian authorized by the IACUC to act in the capacity as a subject matter expert, not as an IACUC member, to review the changes. The veterinarian may request revisions from the PI as necessary and may, at his/her discretion, require full IACUC review of the submission. Once the veterinarian deems the submission acceptable, the submission will be approved and the PI will receive the approval notice.

Significant changes that may not be handled administratively by VVC and must undergo either full committee or designated member review include, but are not limited to:

- A change from non-survival to survival surgery
- Any change resulting in greater pain, distress or degree of invasiveness
- A change in housing or use of animals to a location that is not part of the animal program overseen by the IACUC
- A change in study objectives
- A change in Principal Investigator
- A change that impacts safety of personnel
- A change from a method of euthanasia approved by the AVMA Guidelines for Euthanasia to a method that is not
- Addition of a new procedure type

Related Policies and Guidance documents:

*** Referenced Drugs (see attached Appendix A)**

Drug formularies are lists of drugs that are created and used in a variety of ways. Some drug formularies are general guidance documents, listing acceptable uses, dosages, and routes of administration of a wide variety of drugs that may be administered to animals. As a guidance to changes in anesthesia, analgesia, sedation or euthanasia that can be covered by the VVC, the Brown veterinarians have developed a drug formulary that includes drug regimens that investigators can refer to in their protocols. The VVC process may be used to change the dose, route, concentration, volume, and/or duration of an approved anesthetic, analgesic, or sedative. Should an investigator wish to use an anesthesia, analgesia, euthanasia or sedation protocol that is not represented in the Brown University Animal Care Formulary, published references must be submitted at the time of the request supporting the use of the requested drug or drug combination in the species of interest.

Changes in experimental substances may include use of a different drug, pharmacological agent, peptide inhibitor or antibody etc. that will be used to address the stated overall objective of the approved study. A published reference showing efficacy and the proposed dose/route of administration must be included for this to be considered by VVC.

Appendix A - Formulary

Brown University Lab Animal Formulary

Disclaimer: If you are writing a new protocol or are writing an amendment adding anesthesia or painful/distressful procedures, you MUST consult a veterinarian before submitting.

Definitions

- **Sedation**: A state of mental calmness, decreased response to environmental stimuli, and muscle relaxation. This state is characterized by suppression of spontaneous movement with maintenance of spinal reflexes.
- **Analgesia**: The absence of pain in response to stimulation that would normally be painful. An analgesic drug can provide analgesia by acting at the level of the central nervous system or at the site of inflammation to diminish or block pain signals.
    - Pre-emptive analgesia: Analgesia delivered before the painful stimulus
    - Local analgesia: the loss of pain sensation over a specific area, caused by local administration of a drug that blocks nerve conduction.
    - Multi-modal analgesia: combines 2 or more analgesic agents or techniques that act by different mechanisms to provide analgesia with better pain relief
- **Anesthesia**: central nervous system depression that provides amnesia, unconsciousness and immobility in response to a painful stimulation. Drugs that produce anesthesia may or may not provide analgesia.
    - Injectable anesthesia: a drug or mixture of drugs delivered either intraperitoneally (rodents) or intravascularly (larger animals) to induce and/or maintain anesthesia
    - Inhalant anesthesia: delivery of an inhalant agent (isoflurane) in oxygen directly to the lungs via a face mask or endotracheal tube

<u>The Ideal Anesthetic/Analgesic Regimen</u>

- It should provide pre-emptive analgesia so that animal pain is already being treated as the general anesthetic is wearing off, to prevent sensitization ("ramp-up") of pain sensory mechanisms, and to lower the overall amount of general anesthetic required for the procedure.
- It should be precisely titratable to assure that animals receive adequate anesthesia to block pain sensation, to produce unconsciousness, and to produce immobility without experiencing hemodynamic instability or life-threatening anesthetic overdoses.
- It should not interfere with the study that the animals are on.
- It should not result in unhealthy post-operative side-effects.
- It should not cause pain or distress on induction or recovery
- It should be compatible with available equipment and available medications

Mouse Formulary

Drug Name	Dose (mg/kg) and Route	Frequency	Notes
Inhaled Anesthetic Agents			
Isoflurane*	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Sevoflurane	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Injectable Anesthetic Agents			
Ketamine + Xylazine*	70-100 (K) 5-10 (X) IP in the same syringe	As needed	If redosing, use ketamine alone; may be partially reversed with Atipamezole or Yohimbine
Ketamine + Xylazine + Acepromazine	70-100 (K) 10-15 (X) 2-3 (A) IP in the same syringe	As needed	If redosing, use ketamine alone; may be partially reversed with Atipamezole or Yohimbine
Ketamine + Dexmedetomidine	50-75 (K) 1 (Me) IP in the same syringe	As needed	If redosing, use ketamine alone. May be partially reversed with Atipamezole
Ketamine + Midazolam	70-100 (K) 4-5 (Mi) IP in the same syringe	As needed	May not produce surgical-plane anesthesia for major procedures, but may be useful for restraint
Anesthetic Reversal Agents			
Atipamezole	0.5-1 SC or IP	Any time dexmedetomidine or xylazine has been used	More specific for dexmedetomidine than for xylazine; as a general rule, dose at the same volume as dexmedetomidine
Yohimbine	1-2 SC or IP	For reversal of xylazine effects	
Opioid Analgesia Agents			

Buprenorphine*	0.05-0.1 SC or IP	Use for preemptive analgesia and post-operatively every 4-12 hours	Consider multi-modal analgesia with an NSAID and/or local analgesic

Buprenorphine-SR* (sustained release)	0.5-1 SC	Single dose prior to or at the end of surgery; must give a pre-operative analgesia if giving at the end of surgery	Provides 72 hours of analgesia with single dose; veterinary license required to purchase
Non-Steroidal Anti-Inflammatory Agents (NSAIDs)			
Meloxicam*	2-5 SC or PO	Use for preemptive analgesia and post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Carprofen*	2-5 SC or PO	Use for preemptive analgesia and post-operatively every 12-24 hours	May be used as multi-modal analgesia with an opioid
Ketoprofen	2-5 SC	Use for preemptive analgesia and post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Local Analgesics			
Lidocaine	Dilute to 0.5%, do not exceed 7 mg/kg total dose SC or intra-incisional	Use locally before making surgical incision, or before final skin closure	Faster onset (2 minutes) than bupivacaine but short (<1 hour) duration of action
Bupivacaine	Dilute to 0.25%, do not exceed 8 mg/kg total dose SC or intra-incisional	Use locally before making surgical incision, or before final skin closure	Slower onset (15-20 minutes) than lidocaine but longer (4-8 hours) duration of action

* Denotes the recommended/preferred agent. IP: intraperitoneally; into the peritoneal cavity SC: subcutaneously; under the skin
PO: per os; by mouth

Rat Formulary

Drug Name	Dose (mg/kg) and Route	Frequency	Notes
Inhaled Anesthetic Agents			
Isoflurane*	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Sevoflurane	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Injectable Anesthetic Agents			
Ketamine + Xylazine*	70-100 (K) 5-10 (X) IP in the same syringe	As needed	If redosing, use ketamine alone; may be partially reversed with Atipamezole or Yohimbine
Ketamine + Xylazine + Acepromazine	70-100 (K) 5-10 (X) 1-2 (A) IP in the same syringe	As needed	If redosing, use ketamine alone; may be partially reversed with Atipamezole or Yohimbine
Ketamine + Dexmedetomidine	75-90 (K) 0.5 (Me) IP in the same syringe	As needed	If redosing, use ketamine alone. May be partially reversed with Atipamezole
Ketamine + Midazolam	70-100 (K) 4-5 (Mi) IP in the same syringe	As needed	May not produce surgical-plane anesthesia for major procedures, but may be useful for restraint
Anesthetic Reversal Agents			
Atipamezole	0.5-1 SC or IP	Any time dexmedetomidine or xylazine has been used	More specific for dexmedetomidine than for xylazine; as a general rule, dose at the same volume as dexmedetomidine
Yohimbine	1-2 SC or IP	For reversal of xylazine effects	
Opioid Analgesia Agents			

Buprenorphine*	0.01-0.05 SC or IP	Use for preemptive analgesia and post-operatively every 4-12 hours	Consider multi-modal analgesia with an NSAID and/or local analgesic

Buprenorphine-SR* (sustained release)	1-1.2 SC	Single dose prior to or at the end of surgery; must give a pre-operative analgesia if giving at the end of surgery	Provides 72 hours of analgesia with single dose; veterinary license required to purchase
Non-Steroidal Anti-Inflammatory Agents (NSAIDs)			
Meloxicam*	1-2 SC or PO	Use post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Carprofen*	2-5 SC or PO	Use post-operatively every 12-24 hours	May be used as multi-modal analgesia with an opioid
Ketoprofen	5 SC	Use post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Local Analgesics			
Lidocaine	Dilute to 0.5%, do not exceed 7 mg/kg total dose SC or intra-incisional	Use locally before making surgical incision, or before final skin closure	Faster onset (2 minutes) than bupivacaine but short (<1 hour) duration of action
Bupivacaine	Dilute to 0.25%, do not exceed 8 mg/kg total dose SC or intra-incisional	Use locally before making surgical incision, or before final skin closure	Slower onset (15-20 minutes) than lidocaine but longer (4-8 hours) duration of action

* Denotes the recommended/preferred agent. IP: intraperitoneally; into the peritoneal cavity SC: subcutaneously; under the skin
PO: per os; by mouth

Swine Formulary

Drug Name	Dose (mg/kg) and Route	Frequency	Notes
Inhaled Anesthetic Agents			
Isoflurane*	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Sevoflurane	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Injectable Sedation/Anesthetic Agents			
Ketamine + Xylazine*	20 (K) 1.1-2.2 (X) IM in the same syringe	For sedation or pre-anesthesia	Can result in large volumes
Telazol®* (tiletamine and zolazepam)	6-8 IM	For sedation or pre-anesthesia	Must be reconstituted with sterile water and refrigerated after
Ketamine + Dexmedetomidine	10 (K) 0.05-0.1 (Me) IM in the same syringe	For sedation or pre-anesthesia	
Ketamine + Midazolam	10-15 (K) 0.5-2 (Mi) IM in the same syringe	For sedation or pre-anesthesia	
Telazol® + Xylazine	4-6 (T) 2.2 (X) IM	For sedation or pre-anesthesia	Reconstitute Telazol® with 5 ml of 100 mg/ml xylazine instead of water; must be refrigerated.
Propofol	3-5 IV	Given to effect as induction agent, prior to general anesthesia	Respiratory depression upon induction is possible; no analgesic properties alone
Anesthetic Reversal Agents			
Atipamezole	0.5-1 SC or IM	For reversal of dexmedetomidine or xylazine	More specific for dexmedetomidine than for xylazine; as a general rule, dose at the same volume as dexmedetomidine
Yohimbine	0.05-1 SC or IM	For reversal of xylazine effects	

Opioid Analgesia Agents			
Buprenorphine*	0.05-0.1 SC or IM	Use for preemptive analgesia and post-operatively every 8-12 hours	Consider multi-modal analgesia with an NSAID and local analgesic
Buprenorphine-SR* (sustained release)	0.12-0.2 SC	Single dose at the end of surgery	Provides up to 72 hours of pain relief; consider multi-modal analgesia; veterinary license required to purchase
Butorphanol	0.1-0.5 SC	Use for preemptive analgesia and post-operatively every 4-6 hours	Consider multi-modal analgesia with an NSAID and local analgesic
Oxymorphone	0.15-0.2 IM	Use for preemptive analgesia and post-operatively every 3-4 hours, or for 'rescue analgesia' when buprenorphine is not potent enough	More potent but shorter duration than buprenorphine or butorphanol
Fentanyl transdermal patch	2.5-5 µg/kg/hr	Place 8-12 hours before surgery if possible	Variable absorption; provides 48-72 hours of pain relief
Non-Steroidal Anti-Inflammatory Agents (NSAIDs)			
Meloxicam*	0.2-0.4 PO, IM, or SC	Use post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Carprofen*	2-4 PO, SC, or IM	Use post-operatively every 12-24 hours	May be used as multi-modal analgesia with an opioid
Ketoprofen	1-3 SC	Use post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Local Analgesics			
Lidocaine	2-4 Dilute to 0.5-1% (=10mg/ml). May be mixed in same syringe with bupivacaine SC or intra-incisional	Use locally before making surgical incision	Faster onset (2 minutes) than bupivacaine but short (<1 hour) duration of action

Bupivacaine	1-2 Dilute to 0.25-0.5%, May be mixed in same syringe with lidocaine SC or intra-incisional	Use locally before making surgical incision	Slower onset (15-20 minutes) than lidocaine but longer (4-8 hours) duration of action

* Denotes the recommended/preferred agent.
IM: intramuscularly; into a muscle (the neck or rump) SC: subcutaneously; under the skin (behind the ear)
IV: intravenously; into a vein (must have a patent catheter) PO: per os; by mouth

Nonhuman Primate Formulary (Macaques)

Drug Name	Dose (mg/kg) and Route	Frequency	Notes
Inhaled Anesthetic Agents			
Isoflurane*	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Sevoflurane	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Injectable Sedation/Anesthetic Agents			
Ketamine + Xylazine*	10 (K) 0.5 (X) IM in the same syringe	For sedation or pre-anesthesia	
Ketamine	10-15 IM	For sedation or pre-anesthesia	To be used only for chemical restraint, any invasive procedures require additional drugs
Ketamine + Dexmedetomidine	3-5 (K) 0.03-0.1 (M) IM in the same syringe	For sedation or pre-anesthesia	
Ketamine + Midazolam	8-10 (K) 0.05-0.15 (Mi) IM in the same syringe	For sedation or pre-anesthesia	Midazolam may slightly prolong recovery time, but also makes for smoother recovery
Telazol® (tiletamine and zolazepam)	3-6 IM	For sedation or pre-anesthesia	Must be reconstituted with sterile water and refrigerated after
Propofol	2.5-5 IV	Given to effect as induction agent, prior to general anesthesia	Respiratory depression upon induction is possible; no analgesic properties alone
Anesthetic Reversal Agents			
Atipamezole	0.15-0.2 SC or IM	For reversal of dexmedetomidine or xylazine	More specific for dexmedetomidine than for xylazine; as a general rule, dose at the same volume as dexmedetomidine
Yohimbine	0.2 SC or IM	For reversal of xylazine effects	

Opioid Analgesia Agents			
Buprenorphine*	0.01-0.03 SC or IM	Use for preemptive analgesia and post-operatively every 6-12 hours	Consider multi-modal analgesia with an NSAID and local analgesic
Buprenorphine-SR* (sustained release)	0.2 SC	Single dose at the end of surgery	Provides 3-5 days of pain relief; consider multi-modal analgesia; veterinary license required to purchase
Oxymorphone	0.15 SC or IM	Use for preemptive analgesia and post-operatively every 4-6 hours	More potent but shorter duration than buprenorphine
Non-Steroidal Anti-Inflammatory Agents (NSAIDs)			
Meloxicam*	0.1-0.2 PO, IM, or SC	Use post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Carprofen	2-4 PO or IM	Use post-operatively every 12 hours	May be used as multi-modal analgesia with an opioid
Ketoprofen	2 IM or SC	Use post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Local Analgesics			
Lidocaine	2-4 Dilute to 0.5-1% (=10mg/ml). May be mixed in same syringe with bupivacaine SC or intra-incisional	Use locally before making surgical incision	Faster onset (2 minutes) than bupivacaine but short (<1 hour) duration of action
Bupivacaine	1-2 Dilute to 0.25-0.5%, May be mixed in same syringe with lidocaine SC or intra-incisional	Use locally before making surgical incision	Slower onset (15-20 minutes) than lidocaine but longer (4-8 hours) duration of action

* Denotes the recommended/preferred agent.

IM: intramuscularly; into a muscle (quadriceps or hamstring muscles) SC: subcutaneously; under the skin (anywhere there's loose skin)

IV: intravenously; into a vein (must have a patent catheter) PO: per os; by mouth

Sheep Formulary

Drug Name	Dose (mg/kg) and Route	Frequency	Notes
Inhaled Anesthetic Agents			
Isoflurane*	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Sevoflurane	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Injectable Sedation/Anesthetic Agents			
Ketamine + Xylazine*	4 (K) 0.1 (X) IM in the same syringe	For sedation or pre-anesthesia	
Ketamine + Dexmedetomidine	1 (K) 0.025 (Me) IM in the same syringe	For sedation or pre-anesthesia	
Ketamine + Midazolam	4 (K) 0.5 (Mi) IM in the same syringe	For sedation or pre-anesthesia	
Propofol	4-5 IV	Given to effect as induction agent, prior to general anesthesia	Respiratory depression upon induction is possible; no analgesic properties alone.
Anesthetic Reversal Agents			
Atipamezole	0.1-0.2 IM or IV	For reversal of dexmedetomidine or xylazine	More specific for dexmedetomidine than for xylazine; as a general rule, dose at the same volume as dexmedetomidine
Yohimbine	0.2 SC or IM	For reversal of xylazine effects	
Opioid Analgesia Agents			
Buprenorphine*	0.005-0.01 SC or IM	Use for preemptive analgesia and post-operatively every 8 hours	Consider multi-modal analgesia with an NSAID and local analgesic
Butorphanol	0.1-0.5 IM	Use for preemptive analgesia and post-operatively every 2-4 hours	Consider multi-modal analgesia with an NSAID and local analgesic

Fentanyl transdermal patch	2.-3 µg/kg/hr	Place 8-12 hours before surgery if possible	Provides 48-72 hours of pain relief
Non-Steroidal Anti-Inflammatory Agents (NSAIDs)			
Flunixin*	1-2 IV or IM	Use post-operatively every 12-24 hours	May be used as multi-modal analgesia with an opioid
Meloxicam*	1 IM or PO	Use post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Carprofen	2-4 SC or IM	Use post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Local Analgesics			
Lidocaine	2-4 Dilute to 0.5-1% (=10mg/ml). May be mixed in same syringe with bupivacaine SC or intra-incisional	Use locally before making surgical incision	Faster onset (2 minutes) than bupivacaine but short (<1 hour) duration of action
Bupivacaine	1-2 Dilute to 0.25-0.5%, May be mixed in same syringe with lidocaine SC or intra-incisional	Use locally before making surgical incision	Slower onset (15-20 minutes) than lidocaine but longer (4-8 hours) duration of action

* Denotes the recommended/preferred agent.
IM: intramuscularly; into a muscle (rump or epaxial muscles)
SC: subcutaneously; under the skin (anywhere there's loose skin) IV: intravenously; into a vein (must have a patent catheter)
PO: per os; by mouth

Avian Formulary

Drug Name	Dose (mg/kg) and Route	Frequency	Notes
Inhaled Anesthetic Agents			
Isoflurane*	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Injectable Sedation/Anesthetic Agents			
Ketamine + Xylazine	10-15 (K) 2 (X) IM in the same syringe	For sedation or pre-anesthesia	
Ketamine + Midazolam	10-40 (K) 0.2-2 (Mi) IM in the same syringe	For sedation or pre-anesthesia	
Ketamine + Acepromazine	10-25 (K) 0.5-1.0 (A) IM in the same syringe	For sedation or pre-anesthesia	Use higher end of dose range for birds <250g
Ketamine + Dexmedetomidine	2-6 (K) 0.04-0.15 (D) SC in the same syringe	For sedation or pre-anesthesia	
Anesthetic Reversal Agents			
Atipamezole	0.5 SC	For reversal of dexmedetomidine or xylazine	More specific for dexmedetomidine than for xylazine; as a general rule, dose at the same volume as dexmedetomidine
Opioid Analgesia Agents			
Butorphanol*	0.5-4 IM	Use for preemptive analgesia and post-operatively every 4-6 hours	Recommend analgesic for most species of birds; consider multi-modal analgesia with an NSAID or local anesthetic.
Buprenorphine	0.01-0.05 IM	Use for preemptive analgesia and post-operatively every 8-12 hours	Consider multi-modal analgesia with an NSAID or local anesthetic
Non-Steroidal Anti-Inflammatory Agents (NSAIDs)			
Meloxicam*	0.2-0.3 SC	Use post-operatively every 12-24 hours	May be used as multi-modal analgesia with an opioid

Carprofen	1 SC	Use post-operatively every 4 hours	May be used as multi-modal analgesia with an opioid
Local Analgesics			
Lidocaine	1-3 Dilute to 0.5-1% (=10mg/ml). May be mixed in same syringe with bupivacaine SC or intra-incisional	Use locally before making surgical incision	Faster onset (2 minutes) than bupivacaine but short (<1 hour) duration of action
Bupivacaine	2 Dilute to 0.25-0.5%, May be mixed in same syringe with lidocaine SC or intra-incisional	Use locally before making surgical incision	Slower onset (15-20 minutes) than lidocaine but longer (4-8 hours) duration of action

* Denotes the recommended/preferred agent.
IM: intramuscularly; into a muscle (rump or epaxial muscles)
SC: subcutaneously; under the skin (anywhere there's loose skin)

Reptile Formulary

Drug Name	Dose (mg/kg) and Route	Frequency	Notes
Inhaled Anesthetic Agents			
Isoflurane*	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Injectable Anesthetic Agents			
Ketamine	10-30 (K) SC or IM	As needed	Lower doses may be used to sedate animals for inhalant anesthesia intubation
Ketamine + Dexmedetomidine	5-10 (K) 0.05-0.1 (D) IM in the same syringe	As needed	
Telazol® (tiletamine and zolazepam)	5-10 IM	As needed	Must be reconstituted with sterile water and refrigerated after
Propofol	10 IV	Given to effect as induction agent, prior to general anesthesia	Respiratory depression upon induction is possible; no analgesic properties alone.
Anesthetic Reversal Agents			
Atipamezole	SC	For reversal of dexmedetomidine	Dose at the same volume as dexmedetomidine
Opioid Analgesia Agents			
Buprenorphine	0.01-0.05 IM	Use for preemptive analgesia and post-operatively every 24-48 hours	Consider multi-modal analgesia with an NSAID or local anesthetic
Butorphanol	0.5-2 SC or IM	Use for preemptive analgesia and post-operatively every 24 hours	Consider multi-modal analgesia with an NSAID or local anesthetic
Non-Steroidal Anti-Inflammatory Agents (NSAIDs)			
Meloxicam	0.1-0.5 PO or SC	Use post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Ketoprofen	2 SC or IM	Use post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid

Carprofen	1-4 SC or IM	Use post-operatively every 24 hours	May be used as multi-modal analgesia with an opioid
Local Analgesics			
Lidocaine	2-5 Dilute to 0.5-1% (=10mg/ml). SC or intra-incisional	Use locally before making surgical incision	Fast onset (2 minutes) but short (<1 hour) duration of action

IMPORTANT: All injected medications must be given in the anterior third of the body for snakes, or the front limbs of other reptiles.

* Denotes the recommended/preferred agent.
IM: intramuscularly; into a muscle (epaxial muscles in snakes, upper leg muscles in others) SC: subcutaneously; under the skin (anywhere there's loose skin)
IV: intravenously; into a vein (must have a patent catheter) PO: per os; by mouth

Bat Formulary

Drug Name	Dose (mg/kg) and Route	Frequency	Notes
Inhaled Anesthetic Agents			
Isoflurane*	1-3% to effect (up to 5% for induction)	Whenever general anesthesia is needed	Survival surgery requires concurrent preemptive analgesia
Injectable Anesthetic Agents			
Dexmedetomidine + Midazolam + Fentanyl (MMF)*	0.4 (D) 4 (Mi) 0.04 (F) IM in the same syringe	As needed	
Ketamine + Xylazine	10-15 (K) 2 (X) IM in the same syringe	As needed	
Opioid Analgesia Agents			
Buprenorphine*	0.1 PO	Use for preemptive analgesia and post-operatively every 12 hours	May be applied to the gums to be absorbed through mucous membranes
Tramadol	3.75 PO	Use for preemptive analgesia and post-operatively every 8 hours	Dissolve one 50 mg tablet in 20 mls distilled water
Non-Steroidal Anti-Inflammatory Agents (NSAIDs)			
Meloxicam*	3 PO	Use post-operatively every 12 hours	May be used as multi-modal analgesia with opioid

* Denotes the recommended/preferred agent.
IM: intramuscularly; into a muscle (thigh muscle) PO: per os; by mouth

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Appendix B - Justification for the Use of NPG Compounds

Guidelines for the Use of Non-Pharmaceutical Grade Compounds in Laboratory Animals

Investigators are expected by regulatory authorities to use pharmaceutical grade compounds whenever possible. The Guidelines presented here are a synopsis of the requirements and expectations for the use of non-pharmaceutical-grade compounds (Non-PGCs) when they are necessary. This document references the policies and guidelines of the major animal research oversight organizations.[1-6]

Definitions:

Pharmaceutical-grade compound: A pharmaceutical-grade compound (PGC) is defined as any active or inactive drug, biologic or reagent, for which a chemical purity standard has been established by a recognized national or regional pharmacopeia (e.g., the U.S. Pharmacopeia (USP), British Pharmacopeia (BP), National Formulary (NF), European Pharmacopoeia (EP), Japanese Pharmacopeia (JP), etc.). These standards are used by manufacturers to help ensure the products are of the appropriate chemical purity and quality, in the appropriate solution or compound, to ensure stability, safety, and efficacy.[2] The Food and Drug Administration (FDA) maintains a database listing of FDA approved commercial formulations for both FDA approved human drugs (the Orange Book) and veterinary drugs (the Green Book).

Availability: Refers to compounds that are commercially available from an active U.S. vendor.

New investigational compound: A compound supplied by its manufacturer for testing in an experimental setting only and for this reason would not have chemical purity standards established and by default is considered a non-pharmaceutical-grade compound.

Requirements:

When compounds are used for the clinical treatment of animals or to prevent or reduce/ eliminate animal pain or distress, PGCs must be used whenever possible.[2] When compounds are used to accomplish the scientific aims of the study PGCs are preferred if available and suitable.[2]

The use of Non-PGCs in laboratory animals must be described and justified in the Animal Use Protocol and/or covered by the Animal Care and Use Committee's (IACUC) policy developed for their use.

AAALAC states that the investigator and the IACUC consider the following factors when using Non-PGCs:[2]

- The provided scientific justification such as:
  - A PGC is not available; this includes new investigational compounds.
  - A PGC is not available in the appropriate concentration or formulation or the appropriate vehicle control is unavailable.
  - The Non-PGC is required to generate data that are part of an ongoing study or to generate data that are comparable to previous work.
- Whether the chemical properties of the compound are appropriate for the study and the route of administration (e.g., the purity, grade, stability in and out of solution, solution vehicle properties, pH, osmolality, and compatibility of the solvent and other components of final preparation).
- The method of preparation, labeling (preparation and use-by dates), administration and storage of formulations should be appropriately considered with the aim of

maintaining their stability and quality.

- Use must be compliant with applicable national or regional regulatory guidelines and requirements and the requirements of relevant funding agencies.

The last three factors are not specific to Non-PGCs and therefore should be considered by the IACUC in general terms as is done for all pharmaceuticals and reagents.

Although the potential animal welfare consequences of complications are less evident in non-survival studies, the scientific issues remain the same as in survival studies and therefore apply to non-survival studies. The use of a non-pharmaceutical-grade euthanasia agent must meet the same standards as for use in any other application.[3]

The guidelines pertain to all components, both active and inactive, contained in the preparation to be administered. Therefore, the vehicle used to facilitate administration of a compound is as important of a consideration as the active compound in the preparation. Veterinary and human drugs that are reconstituted in a manner not in accord with the product insert are considered Non-PGCs.

Recommendations for use of non-pharmaceutical-grade compounds:

Where the use of Non-PGCs may be essential for the conduct of science, the goal of the IACUC should be to consider the health and well-being of the animals while aiding the researcher in minimizing potentially confounding experimental variables and maximizing reproducibility of the research.[2]

As stated by Office of Laboratory Animal Welfare, this Guideline suggests that the IACUC, in making its evaluation may consider factors including, for example grade, purity, sterility, acid- base balance, pyrogenicity, osmolality, stability, site and route of administration, compatibility of components, side effects and adverse reactions, storage, and pharmacokinetics.[3] The following should be considered in the order presented for pharmaceuticals and reagents of all kinds prior to use:

1. FDA approved veterinary or human pharmaceutical compounds;
2. FDA approved veterinary or human pharmaceutical compounds used to compound a needed dosage form;
3. USP/NF, BP, or other pharmacopeia recognized PGCs used in a needed dosage form;
4. Analytical grade bulk chemical used to compound a needed dosage form (requires justification);
5. Other grades and sources of compounds (requires justification).

An ACF veterinarian can provide assistance in availability, procurement, and formulation of various PGCs.

The IACUC will consider relevant animal welfare and scientific issues including safety, efficacy, availability of PGCs, and the inadvertent introduction of new variables.[3] Cost savings alone is not an adequate justification for the use of Non-PGCs. However, unavailability or shortages of PGCs may lead to cost increases and necessitate that the IACUC determine whether this justifies the use of the Non-PGC substitution.[6]

Acceptable scientific justifications for the use of non-pharmaceutical-grade compounds:[4]

1. No equivalent veterinary or human drug is available for experimental use. The highest-grade equivalent chemical reagent should be used and formulated aseptically, with a non-toxic vehicle, as appropriate for the route of administration.
2. Although an equivalent veterinary or human drug is available for experimental use, the analytical or chemical grade reagent may be required to replicate methods from previous

studies if it is the only option to produce results that are directly comparable.

3. Although an equivalent veterinary or human drug is available, dilution or change in formulation is required.
    - If the formulation as provided must be diluted, altered by addition, or otherwise changed, there may be no additional advantage to be gained by using the USP formulation.
    - In this situation, use of the highest grade reagent may have the advantage of single-stage formulation and also result in purity that is equal to or higher than the human or veterinary drug.
    - Professional judgment should be used to determine the appropriate test material and to ensure use of an agent with the least likelihood for causing adverse effects.
4. The available human or veterinary drug is not concentrated enough to meet experimental requirements.
5. The available human or veterinary drug does not meet the non-toxic vehicle requirements for the specified route of administration.

References:

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3. OLAW Position Statement- Non-Pharmaceutical-Grade Substances
4. Transcript of OLAW On-line Seminar broadcast on March 1, 2012 - Use of Non-Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals
5. Transcript of OLAW On-line Seminar broadcast on June 4, 2015 - Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals
6. OLAW Frequently Asked Questions – PHS Policy on Humane Care and Use of Laboratory Animals, F. Animal Use and Management, 4. May investigators use non-pharmaceutical-grade substances in animals?