Date: 1 June 2015
Re: Procedures for Compounded Pharmaceuticals (e.g. Buprenorphine-SR; Meloxicam-SR; collectively defined here as CP's)

BACKGROUND: Compounded pharmaceuticals have the potential ability to significantly improve animal welfare while reducing risks to personnel from unintended bites or scratches while administering frequent doses of analgesics. There are two stipulations regarding the use of compounded pharmaceuticals:

1. They are only available from a compounding pharmacy, and
2. They require a prescription from a veterinary practitioner for procurement.

PROCUREMENT PROCESS: At Duke, the process is as follows:
1. The use of CP’s is first approved by the IACUC either in the initial approved animal use protocol or as an approved amendment.
2. The PI will contact ZooPharm and set-up an account for purchase from ZooPharm. The web link is: http://wildpharm.com/zoopharm-home.html
3. The PI will request a prescription from IACUC@DUKE.EDU
4. Dr. Ron Banks (under the veterinary practitioner DEA registration) will write a prescription for purchase of CP’s, as approved in the animal use protocol (or amendment). Each prescription is good for six months and for up to five refills within that six month period.
5. The PI will submit a copy of the prescription to ZooPharm, and ZooPharm will sell the medication to the PI.
6. The PI will receive the medication, record receipt, and maintain log sheets for the use of CP’s.

Note: If the PI is using only CP’s, then there is no need for the PI to obtain a state or federal controlled substance registration. While the use of a prescription for obtaining a compounded product eliminates the federal need for a controlled substance registration, Duke University does require record-keeping for this product in the same manner as with all other controlled substance. See the Controlled Substances Procedure Plan (http://vetmed.duhs.duke.edu/PDF/Policies/Controlled%20Substance/ControlledSubstanceProcedures20120418.pdf) for more details regarding recordkeeping requirements.

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APPENDIX A
BUPRENORPHINE-SR

Buprenorphine produces excellent analgesia in many species, especially 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.

A thebaine derivative with powerful analgesia approximately twenty-five to forty times as potent as morphine, Buprenorphine’s analgesic effect is due to partial agonist activity at the opioid receptors, i.e., when the molecule binds to a receptor, it is only partially activated in contrast to a full agonist such as morphine. Buprenorphine also has very high binding affinity for the μ receptor such that opioid receptor antagonists (e.g. naloxone) only partially reverse its effects.

Buprenorphine is metabolized by the liver, via CYP3A4 (also CYP2C8 seems to be involved) isozymes of the cytochrome P450 enzyme system, into norbuprenorphine (by N-dealkylation). The glucuronidation of buprenorphine is primarily carried out by UGT1A1 and UGT2B7, and that of norbuprenorphine by UGT1A1 and UGT1A3. These glucuronides are then eliminated mainly through excretion into the bile. The elimination half-life of buprenorphine is 20–73 hours (mean 37). Due to the mainly hepatic elimination, there is little risk of accumulation in patients with renal impairment. Buprenorphine's main active metabolite, norbuprenorphine, is a μ-opioid, δ-opioid, and nociceptin receptor full agonist, with a κ-opioid receptor partial agonist. Buprenorphine antagonizes its effects.

Buprenorphine-SR (Lab) is a compounded formulation of Buprenorphine with significant advantage over the original formulation without sustained release. A published study in the Journal of the American Association for Laboratory Animal Science, tested a buprenorphine sustained-release formulation in rats for analgesic efficacy and found plasma concentration over a 72-h time period. Rats were injected subcutaneously with 1.2 mg/kg (Buprenorphine-SR). Buprenorphine-SR showed evidence of analgesia for 2 to 3 days, reporting plasma concentrations of buprenorphine remaining over 1 ng/mL for 72 h after a single dose.

SUPPLIED: Buprenorphine hydrochloride is available from ZooPharm, a compounding pharmacy upon prescription by a veterinary practitioner at a concentration of 3 mg/ml in a 5 ml vial in a sustained release biodegradable matrix.

PRECAUTIONS AND POSSIBLE SIDE EFFECTS: Buprenorphine should be used with caution in animals with head trauma, compromised cardiovascular function, liver disease, geriatric or severely debilitated animals, pregnant or lactating animals, and in very young animals.
Meloxicam is an NSAID of the oxicam class that acts by inhibiting prostaglandin synthesis and inducible COX-2, thereby exerting antiinflammatory, anti-exudative, analgesic and antipyretic effects. The molecule is highly plasma protein bound, when circulating in the body (95-99%). It has a long plasma half-life, providing therapeutic blood levels for up to 72 hours.

Primary pharmacological effects include anti-inflammatory, anti-pyretic and analgesic properties in several species including humans, probably due to inhibition of inducible cyclo-oxygenase. Tissue reactions after a single subcutaneous injection of meloxicam was studied in rats. The conclusions reported from these study data indicated that the meloxicam injectable formulation was well tolerated. Its chemical name is 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

**INDICATIONS:**
Meloxicam is used in dogs, rats, mice, rabbits, primates and other species for relief of inflammation and pain in both acute and chronic musculo-skeletal disorders. Meloxicam is often used to reduce postoperative pain and inflammation following orthopaedic, soft tissue and other surgical procedures.

**PHARMACOKINETICS:**
The pharmacokinetic behavior of meloxicam after a single dose was elucidated in an intravenous pilot study in calves with radiolabelled meloxicam and in a bioavailability study in calves with administration of 0.5% injectable meloxicam solution via the IV and SC route in a cross-over design. The Cmax of meloxicam from the SC administration was reached after 6 to 8 hours. The absolute availability was variable with values ranging from 44 to 154 % in individual animals. The mean elimination half-life of meloxicam from plasma was approximately 26 hours irrespective of the route of administration. Elimination of total radioactivity from plasma exhibited a terminal half-life of approximately 24 hours. Plasma protein binding ex vivo was found to be > 96.5 % and the same degree of binding was found in vitro. At all sacrifice time points investigated in the pilot study, the liver contained the highest concentration followed by the kidney and bile. Comparatively low concentrations