POLICY

TITLE:	Non-pharmaceutical Grade Compounds, Compounded Mixtures or Expired Compounds or Materials
Policy Number:	2014-001
Responsible Department:	Institutional Animal Care and Use Committee
Policy Contact:	IACUCOffice@westernu.edu
Approval Date:	6/11/14
Reviewed:	6/7/17; 1/13/2020
Revised:	10/26/16 (Stability of compounded drugs); 6/7/17 (Added reference to USDA Animal Care Policy #3); 1/13/2020 (Added instructions for reconstituted drugs and AVMA Guidelines for Depopulation of Animals in emergency)
Legislation:	Animal Welfare Act (Title 9 CFR Subchapter A, Part 2, Subpart C, § 2.31-2.33 and Subpart D, § 2.40)

Purpose of Policy: To ensure that adequate veterinary care is provided to all animals used in teaching or research and that the use of all drugs, fluids, sutures or other materials in such animals meets the standards outlined by the Animal Welfare Act;, the USDA Animal Care Policy #3 and the Public Health Service Policy on Humane Care and Use of Laboratory Animals.

Policy Information:

Non-pharmaceutical grade compounds: The *Guide for the Care and Use of Laboratory Animals* states that "pharmaceutical-grade chemicals and other substances" should be used "when available for all animal-related procedures." Section F4, of the Office of Laboratory Animal Welfare's (OLAW) FAQs, in agreement with the United States Department of Agriculture (USDA) and the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC), defines a pharmaceutical grade compound as "a drug, biologic or reagent that is approved by the Food and Drug Administration or for which a chemical purity standard has been established by the United States Pharmacopoeia-National Formulary or British Pharmacopoeia." The Food and Drug Administration (FDA) maintains a database of FDA-approved formulations both for human (Orange Book) and veterinary (Green Book) compounds.

Policy: Pharmaceutical grade compounds must be used whenever possible for all animal-related procedures. In the event that the required pharmaceutical grade compound is not available or that an investigational compound, compounded agent or Schedule I controlled substance for which chemical purity standards have not been established is required, the IACUC will evaluate the potential adverse consequences of such agents and make a determination regarding authorizing its use. Cost savings alone is not adequate justification for the use of non-pharmaceutical grade compounds unless the cost is so great that the IACUC considers the agent unavailable. For example, OLAW has stated that "exorbitant

cost increases of pentobarbital have placed it logistically in the unavailable category". WesternU will also accept as pharmaceutical grade compounds listed in the Japanese Pharmacopoeia.

Powdered forms of drugs or compounds (e.g., chemical grade substances ordered from Sigma) that do not bear an expiration date should be labeled with an expiration date based on best estimates of similar drugs or compounds. For drugs or solutions that are reconstituted for use, the stability of the compounds may change and, therefore, the expiration dates may vary from the expiration dates of the powdered forms. For reconstituted drugs and compounds that do not contain expiration or efficacy guidance in the labeled directions, investigators should use their best judgement in determining an appropriate expiration date.

Compounded mixtures: If a drug is removed from the manufacturer's original container and mixed into a cocktail or with some other vehicle or is placed in a container other than the manufacturer's original container, the new container must be sterile and labeled with the expiration date of the soonest expiring ingredient along with the name of each drug in the mixture, their concentrations, and the name or initials of the person who prepared the mixture.

If none of the ingredients have an expiration date, a "beyond use date" (BUD) of three (3) months from the date of preparation is recommended. BUD is defined as "*…the end of that period of time over which an extemporaneously compounded drug has been shown to remain free of interactions between its individual component drugs and free of changes to its sterility and physical condition*".

This BUD is adopted based on a stability study of a commonly used mixture of ketamine, xylazine and acepromazine (Can J Vet Res. 2016 Jan; 80(1):86-9). However, a shorter or longer time frame may be appropriate depending on the compounds(s) and diluent(s), the frequency of vial entry and the stability, efficacy and safety of the compounds(s) upon storage.

Additionally, if compounds are formulated from non-sterile or sterile powders or solutions obtained from a chemical company or compounded in a research laboratory, then toxic impurities must be minimized and the highest purity compound must be used. When diluents from a pharmaceutical company, pharmacy, or research laboratory must be used, then the solution must be passed through a 0.22 micron filter and stored in a sterile vial. Drugs to be administered orally or administered to aquatic habitats need not be sterile or diluted with pharmaceutical grade substances.

When making drug dilutions, use aseptic technique and make only what is needed. Sterile needles, syringes and containers must be used. Multi-use vials should be disinfected prior to each use by swabbing the rubber cap with alcohol. Use amber containers if the mixture contains ingredients sensitive to light (e.g. buprenorphine and carprofen). As with compounded mixtures, drug dilutions must contain the drug name and concentration, the BUD, storage conditions and name or initials of the preparer.

Unused solutions should be kept refrigerated (4° C) provided that the stability of the mixture is not affected by cold temperatures. Mixtures that have become discolored or that become cloudy or develop a precipitate should be immediately discarded.

The following is a list of medications or mixtures of medications for which the three month BUD does not apply.

- Carprofen (analgesic, anti-inflammatory agent) – BUD: 7 days after dilution; unstable; light sensitive – use amber container; keep refrigerated
- Propofol (anesthetic) – BUD: discard unused volume immediately; prone to bacterial contamination

Contact the Attending Veterinarian for further guidance if needed.

Expired drugs: The USDA Animal Care Policy #3 states that "The use of expired medical materials…during any survival surgical procedure on a regulated species is not considered acceptable veterinary practice and therefore not consistent with adequate veterinary care as required by the regulations promulgated under the Animal Welfare Act." Section F5, of OLAW's FAQs states that "The use of expired pharmaceuticals, biologics and supplies is not consistent with acceptable veterinary practice or adequate veterinary care." However, the 2019 American Veterinary Medical Association (AVMA) Guidelines for the Depopulation of Animals states that "When rapid depopulation of large rodent colonies is necessary" and "…when the time to depopulate is restricted, such as in an impending natural disaster, the Attending Veterinarian (AV) may use professional discretion in forgoing some of the conditions imposed in the AVMA Guidelines for the Euthanasia of Animals". Similar language is repeated in the Guidelines for each type of animal species mentioned. The Guidelines further state that the "Use of compounded or non-pharmaceutical-grade injectable anesthetics and euthanasia agents is justified for depopulation. In addition, an AV may make a professional judgment about the use of agents that have exceeded their product expiration date. If the AV determines the expired product to perform in the expected manner, he may direct its use for depopulation."

Policy: The use of expired anesthetics, analgesics, euthanasia or emergency drugs in any animal-related procedure is not allowed. Expired drugs, other than those in the categories listed above, and expired materials, such as sutures, may only be used on dead animals, anesthetized animals undergoing a terminal procedure from which they will not recover, or to depopulate animals of any species in light of an impending natural disaster provided that, in the professional opinion of the AV, the expired product will perform in the expected manner. All expired materials must be labeled as such and kept separate from other materials.