

University of Colorado Boulder
Office of Research Integrity
Institutional Animal Care and Use Committee
SOP # 10

Use of Drugs, Solutions, Materials and Biologics in Animals

PURPOSE

This standard operating procedure describes the requirements for using drugs, solutions, materials, and biologics in vertebrate animals and describes procedures for preparation, labeling, inventory, and disposal in order to be in compliance with the regulations and guidelines referenced at the end of this SOP.

DEFINITION

A pharmaceutical-grade compound is a drug, biologic, or reagent that is approved by the Food and Drug Administration (FDA) or for which a chemical purity standard has been established by a recognized national or regional pharmacopeia (e.g., the United States Pharmacopeia (USP)-National Formulary (NF), British Pharmacopeia (BP), European Pharmacopoeia (EP), etc.).

A. GENERAL POLICY

- i. In accordance with the Office of Laboratory Animal Welfare (OLAW), pharmaceutical-grade chemicals, drugs, and other substances including diluents must be used whenever available and appropriate to avoid unwanted side effects. Food-grade diluents must be used whenever possible for oral administration.
- ii. Drugs used for sedation, anesthesia, analgesia, euthanasia, or other treatment of disease or injury must be a human or veterinary pharmaceutical-grade compound. A standing exception is in the case of sodium pentobarbital. OLAW states that non-pharmaceutical grade sodium pentobarbital as well as Euthanasia Solutions such as Fatal Plus, Euthasol, Beuthanasia, and Somlethal (which are non-sterile) can only be utilized for euthanasia.
- iii. Pharmaceuticals for use in animals may not be expired, even for terminal procedures.

B. POLICY FOR THE USE OF NON-PHARMACEUTICAL GRADE SUBSTANCES AND MATERIALS

- i. The use of non-pharmaceutical grade substances must be approved by the IACUC in cases of scientific necessity and/or non-availability of acceptable pharmaceutical grade alternatives. Cost savings is not an adequate justification for using non-pharmaceutical grade compounds, drugs, and materials in animals.
- ii. The IACUC may consider grade, purity, sterility, acid-base balance, pyrogenicity, osmolality, stability, site and route of administration, compatibility of components, side effects, adverse reactions, storage, and pharmacokinetics when making an evaluation of non-pharmaceutical grade chemicals, materials, drugs, and biologics proposed for use in animals.
- iii. Specific CU Boulder policies on certain non-pharmaceutical grade substances:
 - Refrigerated Tribromoethanol (formerly called Avertin®) must be replaced every 14 days after it is mixed for use in animals. See [SOP #26](#) for further details.
 - The injectable anesthetic combination of ketamine, acepromazine, xylazine (KAX) has been shown to be safe, stable, and efficacious for at least 180 days after mixing if stored in a dark, room-temperature environment. KAX preparation and expiration must still follow the guidelines in the next section.

C. PREPARATION AND EXPIRATION

- i. The use of a non-sterile substance in animals must be justified in an animal use protocol.

- ii. Products with known expiration dates should be utilized before they expire. Pharmaceuticals should be discarded 30 days after compounding or once one component of the mixture has expired, whichever happens sooner. This is an issue of stability, sterility and efficacy.

D. LABELING & STORAGE

- i. All drugs, dilutions, mixtures, compounds, and biologics must be clearly labeled in English with the lab they belong to, compound name, concentration, preparation date, and expiration date if applicable.
- ii. When available, substances should be stored in accordance with manufacturer's instructions.
- iii. When substances, medical materials and supplies are stored in common use areas, they should be labeled with expiration dates and the PI's name. Items not individually labeled must be kept in a drawer, bin, cabinet or other container clearly labeled with the PI's name.
- iv. Do not store expired, unlabeled, or undated materials in common use areas unless they are clearly marked with "NOT FOR USE IN LIVE ANIMALS."
- v. If possible all drugs, compounds, materials, biologics, and supplies should be stored in one location.
- vi. Controlled substances must be stored in a locked unmovable container in accordance with the UCB Policy on the use of Controlled Substances <http://www.colorado.edu/vcr/controlled-substances> and in accordance with DEA regulations.

E. INVENTORY

- i. Establish an inventory system that enables the efficient use and tracking of drugs and medical supplies.
- ii. Special inventory procedures are required for DEA-controlled substances. See <http://www.colorado.edu/vcr/controlled-substances/policies-guidelines> for information.
- iii. It is recommended that you assign inventory responsibilities in your laboratory.

F. DISPOSAL

- i. Researchers are expected to know and understand the proper way to dispose of all substances used in the laboratory. Any questions, contact CU Boulder Environmental Health and Safety (EH&S) department.
- ii. Make sure all substances for disposal are clearly labeled while they await pickup.
- iii. *DISPOSAL RESOURCE*: Non-DEA-controlled drugs, solutions, and unused reagents must be disposed through the EH&S hazardous waste program by completing a hazardous waste tag. If you have any questions, call: 303-492-7845.
- iv. *DISPOSAL RESOURCE*: Controlled substances can be disposed at no cost to the PI by calling the EH&S Hazardous Materials Program Manager Mark Lapham at 303-492-8531; mark.lapham@colorado.edu. For more details see the EH&S guidance document on "[Disposal of controlled substances and other pharmaceuticals](#)".

RECOMMENDATIONS

- i. Purchase or use small volumes of solutions such as sterile pharmaceutical grade saline so that the volume can be utilized within 30 days and access to the same vial can be limited.
- ii. Precautionary measures to reduce toxicity and bacterial infection in solutions include disinfecting the access point (e.g. alcohol swabbing of the rubber stopper), accessing with sterile needles and instruments, tracking the number of uses, utilizing a non-pyogenic, percutaneous compatible preservative, and/or performing quality control measures to ensure consistent sterility and pharmacokinetics.

- iii. Utilize a biosafety cabinet if available for the preparation of solutions.
- iv. Use sterile filters when practical.
- v. Multi-access vials increase the risk of introducing unwanted pathogens into solution, so consider the risk of inserting a needle repeatedly into a rubber stopper.
- vi. Perform regular monthly checks of your inventory.
- vii. Ask your suppliers if they will accept the return of expired materials for credit.
- viii. If a drug, solution, material, or biologic remains efficacious at low temperatures, sterile, frozen aliquots may be prepared and stored. Precautions should be made to reduce the risk of introducing contaminants into your substances by limiting the frequency of access and freeze/thaw cycles.
- ix. For all substances, it is important to maintain a standard of efficacy. If there are any indicators (visual, olfactory) that a product or substance is no longer safe for use in animals, it **must be discarded**.

REFERENCES

- [1] USDA. 2014. APHIS Policy #3, "Veterinary Care" (March 14). Available at http://www.aphis.usda.gov/animal_welfare/downloads/policy/Policy%203%20Final.pdf accessed July 14, 2014.
- [2] Guide for the Care and Use of Laboratory Animals, 8th Edition, page 31.
- [3] PHS Policy IV, C, 1, a-b.
- [4] NIH Position statement on non-pharmaceutical grade compounds, May 2012: http://grants.nih.gov/grants/olaw/positionstatement_guide.htm
- [5] U.S. Drug Enforcement Administration <http://www.deadiversion.usdoj.gov/21cfr/21usc/index.html>
- [6] NIH Office of Laboratory Animal Welfare: <http://grants.nih.gov/grants/olaw/faqs.htm#f4>
- [7] Taylor, B.J., et. al. 2009. Beyond-Use Dating of Extemporaneously Compounded Ketamine, Acepromazine, and Xylazine: Safety, Stability, and Efficacy over Time. Journal of the American Association for Laboratory Animal Science 48:6 pages 718-726
- [8] OLAW FAQs, F. Animal Use and Management http://grants.nih.gov/grants/olaw/faqs.htm#useandmgmt_5
- [9] Title 21, CFR 1300-1308 <http://www.colorado.edu/vcr/controlled-substances>