This IACUC guideline was created to provide guidance to investigators and to set clear expectations on the administration of experimental substances to animals, including the conditional use of non-pharmaceutical-grade substances. This document also clarifies the record keeping, storage, and labeling procedures for all laboratories administering non-pharmaceutical-grade or controlled substances to animals.

All experimental substances administered to animals must be listed in the animal protocol (i.e., table 12 of the protocol application form) for IACUC review. Similarly, the addition of a new (i.e., not in the original protocol) experimental substance to an approved protocol requires IACUC review, as does any significant change\(^1\) to a protocol. However, in order to provide for a timely review while ensuring animal welfare, this proposed significant change may be handled administratively in consultation with the Attending Veterinarian (AV), if all of the following conditions apply:

1. The administration of the new experimental substance doesn't result in greater pain or distress to the animal.
2. The addition of a new experimental substance fits within the study objectives of the protocol, and doesn't involve the addition of a new experimental procedure.
3. The experimental substance being added to the protocol is administered to animals according to a dose and route of administration that conforms to an established veterinary drug formulary and practice, and/or FDA Guidance on inter-species dose translation\(^2\) or appropriate reference in the scientific literature.
4. The formulation, storage and labeling of the experimental substance, if it's not a pharmaceutical-grade substance as defined below, will conform to the procedures for using non-pharmaceutical-grade substances that are also described below.
Relevant Federal Regulations and Guidance:

The Office of Laboratory Animal Welfare (OLAW)\textsuperscript{3-5}, Office of Extramural Research NIH, and Animal and Plant Health Inspection Service (APHIS)\textsuperscript{6}, United States Department of Agriculture (USDA) have clarified the following requirements regarding the use of non-pharmaceutical-grade substances and expired drugs or medical materials:

1. Pharmaceutical-grade substances, when available, must be used to avoid toxicity or side effects that may threaten the health and welfare of vertebrate animals and/or interfere with the interpretation of research results.

2. A pharmaceutical-grade substance is any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices (GMP) which is approved, conditionally approved, or indexed by the Food and Drug Administration (FDA) or for which a chemical purity standard has been written or established by a recognized compendia (e.g., United States Pharmacopeia-National Formulary (USP-NF), British Pharmacopeia (BP)).

3. The IACUC is responsible for evaluating the potential adverse consequences of non-pharmaceutical-grade substances when used for research.

4. The use of expired pharmaceuticals, biologics, and supplies is not consistent with acceptable veterinary practice or adequate veterinary care. Euthanasia, anesthesia and analgesia agents should not be used beyond their expiration date, even if a procedure is terminal. Other expired materials should not be used unless the manufacturer verifies efficacy beyond the expiration date, or the investigator is able to document to the satisfaction of the IACUC that such use would not negatively impact animal welfare or compromise the validity of the study. The veterinarian and IACUC must maintain control over the use of expired medical materials in order to meet their responsibilities to avoid or minimize discomfort, pain or distress to animals.

IACUC Expectations:

In order to protect animal welfare, due consideration must be given to the preparation (grade, purity, sterility, biocompatibility, and stability) and storage of any experimental substance that is administered to animals. Approval for the use of non-pharmaceutical-grade substances will be made on a case-by-case basis by weighing the potential adverse consequences to the animal against scientific criteria for the use of these substances. “Cost savings alone are not an adequate justification for the use of non-pharmaceutical-grade substances in animals. However, unavailability or shortages of pharmaceutical-grade substances may lead to cost increases and the IACUC may determine that this justifies the use of the non-pharmaceutical-grade substitution.”\textsuperscript{3, 4}

The IACUC recommends the following procedures for preparing, storing and labeling non-pharmaceutical-grade experimental substances:

- Use chemicals of the highest grade and purity.
- Use only sterile and biocompatible (physiological pH and osmolality) solutions to dissolve or dilute the non-pharmaceutical-grade experimental substances.
• Use appropriate precautions to prevent microbial contamination when preparing non-pharmaceutical-grade substances, such as aseptic handling and working in a biological safety cabinet. Sterilize all drug solutions prior to parenteral (i.e. IV, IP, IM, or SC) administration. Use of a syringe-top filter (0.2 µm) is recommended for solutions that cannot be sterilized by other methods.

• If information is not available on the chemical stability of the specific experimental substance, then any water-containing formulation of that substance should be used as soon after preparation as possible, but not later than 14 days after preparation when stored at cold temperatures between 2-8°C.

• All experimental substances should be labeled with a preparation and use by date.

The acquisition, storage, and research use of controlled substances (e.g. ketamine, pentobarbital, or cocaine) must conform to DEA regulations and the Best Practices Guide from the UC Office of the President (BUS 50), and in the future the UCSB Controlled Substance Program administered by EH&S. At a minimum, all controlled substances should be securely stored; each drug vial or container should be uniquely identified and clearly labeled with the name, concentration, and expiration date of the drug; and the research use of controlled substances should always be properly documented to enable audit tracking by UCSB officials (i.e. IACUC or EH&S) or federal agents (i.e. DEA or USDA). Further, it is recommended that the following information should be documented: the name of the drug, date of use, brief description of use (e.g. anesthesia, or euthanasia), species and number of animals dosed, amount of drug used, calculated balance of drug remaining in the vial, and the initials of the individual dispensing and administering the drug.

**Resources for Locating Pharmaceutical-Grade Substances for In-Vivo Use**

**Online**

- DailyMed
- FDA Orange Book, which list approved human drug products.
- Animal Drugs @ FDA

**Publications**

Pharmaceuticals for use in humans and animals: *Physician’s Desk Reference* (which is also accessible electronically) and the *Veterinary Pharmaceuticals and Biologicals*, and a search on a web search engine may provide a monograph for any compound labeled for human or animal use. It is suggested that both these resources be considered. Drug monographs will also list brand names with formulations and concentrations that are offered.

**Reference:**

3. OLAW Webinar: "Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals - June 4, 2015"
4. OLAW FAQ: "May investigators use non-pharmaceutical-grade substances in animals?"
5. OLAW FAQ: “May investigators use expired pharmaceuticals, biologics, and supplies in animal?”