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**UC Davis  
Institutional Animal Care and Use Committee (IACUC)**

**Title: Use of Non-Pharmaceutical Grade Compounds in Animals**

**I. Purpose:**

To define the policy regarding the use of non-pharmaceutical grade compounds in animals.

**II. Definition:**

A pharmaceutical grade compound/chemical is an active or inactive drug, biologic, reagent, or adhesive/bonding agent which is approved by the FDA (e.g., Dermabond) or for which a chemical purity standard (e.g., Vetbond) has been established by any recognized pharmacopeia such as: US Pharmacopeia (USP), National Formulary (NF), British Pharmacopeia (BP), or Pharmacopoeia of the Council of Europe (EP). New investigational compounds are not considered pharmaceutical grade because they are manufactured for research studies only and therefore do not have established chemical purity standards.

Pharmaceutical-grade products will include the recognized pharmacopeia on their label such as “USP” indicated on this Ketamine label:



### III. **Background:**

The Office of Laboratory Animal Welfare (OLAW) and the U.S. Department of Agriculture (USDA) state that the use of non-pharmaceutical grade compounds must be based on scientific necessity or non-availability of an acceptable veterinary or human pharmaceutical grade compound. Non-pharmaceutical grade chemical compounds may only be used in animals after specific review and approval by the IACUC. **Compounds that state on the Certificate of Analysis “not for use in humans or animals” may not be used.**

Investigators and IACUCs should consider relevant animal welfare and scientific issues including safety, efficacy, and the inadvertent introduction of confounding variables. Regulatory agencies address standards for sterility, pyrogenicity, stability, pharmacokinetics, and quality control when monitoring pharmaceutical grade manufacturing. This is not necessarily the case for substances produced commercially as reagent grade, or substances produced in a research laboratory or core facility. The approved use of non-pharmaceutical grade compounds is a necessary and acceptable component of biomedical animal research, provided steps are taken to ensure compound sterility and purity prior to use in animals. If there are reasons a compound cannot be purified or sterilized, then justification and preparation methods must be presented in the Animal Care and Use Protocol for the IACUC to review.

### IV. **Policy:**

It is the IACUC's policy to apply the above standards to all live, vertebrate animal research and teaching with animals covered under UC Davis Animal Care and Use Protocols.

It is the PIs responsibility to ensure the correct compounds are used or justified appropriately. If there are questions or clarifications regarding the suitability of a compound contact the IACUC office.

***When selecting compounds the following order of choice should be applied:***

1. FDA approved veterinary or human pharmaceutical compounds.
2. FDA approved veterinary or human pharmaceutical compounds used to compound a needed dose.
3. USP/NF or BP pharmaceutical grade compound used in a needed dose.
4. Analytical grade bulk chemical used to compound a needed dose (requires justification).
5. Other grades and sources of compounds including reference standards (requires justification).

NOTE: For new investigational drugs the grade and formulation are not optional, but the investigator and IACUC can verify health and safety issues described below.

**Non-pharmaceutical-grade Compounds** can only be used in research activities utilizing

animals if reviewed and approved by the IACUC. This includes all compounds administered to animals including drugs and their components (including diluents). One of the following circumstances should be met for consideration by the IACUC:

1. The research activity requires the use of non-pharmaceutical-grade compounds for reason of scientific necessity.
2. Acceptable veterinary or human pharmaceutical-grade products are not available (most novel compounds are in this category).
3. An equivalent veterinary or human drug is available for experimental use; however, the chemical-grade reagent is required to replicate methods from previous studies because results are directly compared to those of replicated studies.
4. The available human or veterinary drug is not concentrated enough to meet experimental requirements or the correct formulation for the route of administration.
5. The available human or veterinary drug contains preservatives or inactive ingredients which confound the research goals of the study.

To further clarify, non-pharmaceutical grade compounds **cannot be used** in research or teaching animals unless all the following criteria are met:

1. Scientific necessity (includes preclinical testing of agents for potential future human use).
2. The test article or compound is not available in the required concentration or formulation, or availability is unreliable as veterinary grade or pharmaceutical grade, and there are no suitable alternatives.
3. The use is described in the Animal Care and Use Protocol and is approved by the IACUC.

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 a non-pharmaceutical grade substitution.

Reconstituted compounds must be labeled with the name of the compound, the date the compound was prepared, concentration, and the expiration date.

Non-pharmaceutical dry powder compounds that do not have an expiration date indicated on the container must be stored in accordance with the manufacturer's recommendations. For compounds to be administered to animals, there must be a method or procedure in place to validate effectiveness if stored for extended periods of time.

Non-pharmaceutical grade compounds must go through a purification or sterilization process, such as filter sterilization through a 0.2  $\mu\text{m}$  filter (pictured below), unless administered orally, rectally, or topically, or unless otherwise indicated in the approved IACUC protocol. Tattoo ink, while not available in pharmaceutical grade, can be used, but special attention must be paid to prevent contamination of the original container.



Aseptic techniques must be used during preparation to avoid contaminants that could result in adverse events and/or negatively impact the research outcome. If the product does not use a buffered and/or isotonic diluent or vehicle, a veterinary consultation must occur.

If the test article or compound has been prepared at the required level and has a certificate of analysis indicating preparation under sterile conditions, testing for sterility, and assessed for contaminants (e.g., endotoxin, mycoplasma) then additional testing for contaminants and sterility may not be required, but should be considered prior to administration.

For viral (e.g., adeno-associated virus, lentivirus, adenovirus) or nonviral vectors considered for use (e.g., gene transfer, immunization) which are typically not pharmaceutical grade (e.g., GMP manufactured) a certificate of analysis from the supplier (e.g., core or similar) must certify that the aliquots provided were prepared under sterile conditions and tested for contaminants such as endotoxin. If not documented and/or tested for sterility and endotoxin by the PI or designee, then the aliquots will require filter sterilization as noted above to avoid adverse events, or must provide scientific justification.

Non-pharmaceutical grade adhesives/bonding agents that will be used directly on animals should be included on IACUC proposals. While sterilization processes may not be appropriate for many materials, processes for ensuring tissue compatibility and sterility/antimicrobial properties should be addressed.

Non-pharmaceutical grade, non-sterile, euthanasia solutions approved for veterinary use (including Pentobarbital and KCL) may be used for euthanasia purposes, but not for anesthesia purposes unless scientifically justified. KCL must only be used on

anesthetized animals. The dose must be a euthanasia dose (i.e.,  $\geq 100$  mg/kg for Pentobarbital, saturated KCL).

Researchers that propose to use non-pharmaceutical grade Sodium Pentobarbital for anesthesia, in addition to the above requirements, must also adhere to the following policy: [“Use of Non-Pharmaceutical Grade Sodium Pentobarbital for Anesthesia of Laboratory Animals”](#).

## V. Resources

1. ILAR, Guide for the Care and Use of Laboratory Animals  
<http://nap.edu/12910>
2. Animal Welfare Act and Regulations  
<https://www.nal.usda.gov/awic/animal-welfare-act>
3. OLAW FAQ  
[http://grants.nih.gov/grants/olaw/faqs.htm#useandmgmt\\_4](http://grants.nih.gov/grants/olaw/faqs.htm#useandmgmt_4)
4. IACUC-44 “Use of Non-Pharmaceutical Grade Sodium Pentobarbital for Anesthesia of Laboratory Animals”  
<https://research.ucdavis.edu/wp-content/uploads/IACUC-44-.pdf>
5. Wayne State University “Use of Non-Pharmaceutical Grade Drugs”  
<https://research.wayne.edu/iacuc/non-pharmaceuticalgradedrugs>