Non-Pharmaceutical Grade Compounds
IACUP Policy
Effective Date: January 2023

UCSF Office of Research
Institutional Animal
Care and Use Program

This policy summarizes standards of review for the IACUC to ensure optimal animal welfare when the use of non-pharmaceutical grade compounds is proposed, as these compounds can present some risk due to concerns over consistency, contamination, or preparation.

Investigators are expected to use pharmaceutical-grade compounds[1] whenever they are available, even in non-survival procedures. Non-pharmaceutical-grade substances should only be used in animals after specific justification, review and approval by the IACUC. *Guide for the Care and Use of Animals, Eighth Edition*, p. 31

Selection of Compounds for Use in Research:
When selecting compounds, the following order of choice should be applied:

1. FDA approved veterinary or human pharmaceutical compounds; The Food and Drug Administration (FDA) maintains a database listing of FDA approved commercial formulations for both FDA approved human drugs (the Orange Book) and veterinary drugs (the Green Book).

2. FDA approved veterinary or human pharmaceutical compounds used to compound a needed dosage form; i.e. FDA approved veterinary or human pharmaceutical compounds that have been diluted or mixed with other FDA-approved compounds in order to be delivered at the appropriate dose and/or volume for a given species.

3. USP/NF or BP pharmaceutical grade compounds used in a needed dosage form; A pharmaceutical grade compound recognized by USP will bear the initials “USP” after the name of the compound.

4. Analytical grade bulk chemical (> 95% pure by weight of the active chemical) used to compound a needed dosage form (requires justification).

5. Other grades and sources of compounds (requires justification).

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[1] **Pharmaceutical Grade Compound:** Pharmaceutical grade drugs will have a National Drug Code (an NDC) that can be found on the packaging. 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 the United States Pharmacopeia-National Formulary (USP-NF), or British Pharmacopeia (BP). When available, all of the components and diluents should be pharmaceutical grade (e.g., pharmaceutical grade sterile water or saline for dilution), include use of techniques to maintain sterility when mixing and storing agents (e.g., sterile rubber stopped vials), and solutions properly labeled to identify the agent(s), dilution/concentration, and expiration date according to IACUC Expired Drugs and Medical Materials Policy. These adulterated solutions do not require separate justification within the IACUC protocol for use.

Considerations for approval of Non-Pharmaceutical-Grade compounds for use in research:
When developing and reviewing a proposal to use non-pharmaceutical grade compounds, the investigator and IACUC will consider animal welfare and scientific issues related to the use of the compounds, including potential for contamination, safety, efficacy, and the inadvertent introduction of confounding research variables.

When the use of non-pharmaceutical-grade substances is proposed, the IACUC should consider the following factors: grade/purity, formulation of the final product, quality control, sterility and factors that may contribute to adverse effects such as, but not limited to, pyrogenicity, stability, pH, osmolality, site/route of administration, pharmacokinetics, and physiological compatibility.

Appropriate justification:
The use of non-pharmaceutical-grade compounds in animal subjects (including experimental compounds) may be acceptable under certain circumstances, based on:

- Non-availability of an acceptable veterinary or human pharmaceutical-grade compound;
- Pharmaceutical grade formulation is not appropriate for dosing in the intended species;
- Non-availability of an acceptable alternative pharmaceutical-grade compound;
- Scientific justification

Cost savings alone is not a justification for using non-pharmaceutical grade compounds in laboratory animals. Sterile diluents and non-toxic vehicles must be used in the preparation of all non-pharmaceutical grade compounds.

Commonly used non-pharmaceutical grade compounds:

1. **Pentobarbital sodium**
   Pharmaceutical grade pentobarbital has been placed logistically into the unavailable category. Pentobarbital from a reagent or analytical-grade powder, properly prepared by a pharmacist or other knowledgeable individual (e.g., chemist, veterinarian, researcher), with assurance of appropriate storage and handling, and approval by the IACUC is acceptable.

2. **Tribromoethanol (Avertin®)**
   Avertin® is the trade name for the injectable anesthetic 2,2,2-tribromoethanol. Avertin® was once manufactured as a pharmaceutical-grade drug, but it is no longer available. See the IACUC Guidelines on Avertin.

3. **Tricaine methanesulfonate (TMS, MS-222®, Tricaine®-S, Finquel®)**
   Tricaine methanesulfonate is the anesthetic of choice for immersion anesthesia for most fish and amphibian species. It is currently available as a pharmaceutical-grade compound under the trade names Finquel® or Tricaine®-S. Investigators are expected to use pharmaceutical grade TMS, unless scientific justification is provided and approved by the IACUC.

4. **Urethane, α-chloralose, and chloral hydrate**
   a. Urethane, α-chloralose, and chloral hydrate have been used as injectable anesthetic agents in laboratory animals, particularly rodents. They are not available as pharmaceutical-grade compounds. Although pharmaceutical-grade alternative anesthetics are available, urethane, α-chloralose, and chloral hydrate still have important roles as anesthetic agents in biomedical research due to unique physiologic effects (for example, urethane has minimal respiratory effects).

b. Scientific justification should be provided for the use of urethane, α-chloralose, or chloral hydrate instead of commercially available, pharmaceutical grade injectable anesthetics.
c. Use of urethane, α-chloralose, and chloral hydrate should be limited to terminal procedures in mammals.
d. Urethane is considered a carcinogen and mutagen. Preparation, use, and disposition of this compound should take into account these hazards, and appropriate safety precautions should be reflected in the IACUC protocol, approved by Environmental Health & Radiation Safety, and implemented by laboratory personnel.

5. New Investigational Compounds:

New investigational compounds may be produced by a laboratory or supplied by a manufacturer for testing in an experimental setting only. Chemical purity standards are generally not established yet. Therefore, new investigational compounds are considered to be non-pharmaceutical grade with no available human or veterinary pharmaceutical grade equivalent or alternative.

References:

a. NIH Office of Animal Care and Use, Guidelines for the Use of Non-Pharmaceutical Grade Compounds in Laboratory Animals
b. United States Pharmacopeia-National Formulary (USP-NF)
c. British Pharmacopeia
d. FDA Drug Approval Database
e. AVMA Euthanasia Guidelines, 2020
f. Katz EM, Chu DK, Casey KM, Jampachaisri K, Felt SA, Pacharinsak C. The Stability and Efficacy of Tricaine Methanesulfonate (MS222) Solution After Long-Term Storage. J Am Assoc Lab Anim Sci. 2020 Jun 12;59(4):393–400. doi: 10.30802/AALAS-JAALAS-19-000067. Epub ahead of print. PMID: 32532365; PMCID: PMC7338872.