

**University of California, Merced**  
**Institutional Animal Care and Use Committee Policy**

Version No. 1

Policy No. 121

## **Pharmaceutical Grade Compounds**

### **I. Purpose:**

This policy describes the use of pharmaceutical grade and non-pharmaceutical grade substances in vertebrate animals.

### **II. Background:**

#### NIH Office of Laboratory Animal Welfare (OLAW)

*Pharmaceutical Grade Compound:* “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)).”

#### USDA: Policy #3, Pharmaceutical-Grade Substances

“Pharmaceutical-grade substances are expected to be used whenever they are available, even in acute procedures. This includes but is not limited to: compounds, medications, drugs, vehicles, and diluents. APHIS recognizes that some substances (e.g. test articles, novel compounds, and those resulting from a compounding process) are only available as a non-pharmaceutical grade product.”

#### The Guide (p31): Use of Non-Pharmaceutical-Grade Chemicals and Other Substances

“The use of pharmaceutical-grade chemicals and other substances ensures that toxic or unwanted side effects are not introduced into studies conducted with experimental animals. They should therefore be used, when available, for all animal-related procedures.”

#### AAALAC—International (FAQ): Non-Pharmaceutical-Grade Compounds

“A pharmaceutical-grade compound is defined as any active or inactive drug, biologic or reagent, for which a chemical purity standard has been established by a recognized national or regional pharmacopeia (e.g., the U.S. Pharmacopeia (USP), British Pharmacopeia (BP), National Formulary (NF), European Pharmacopoeia (EP), Japanese Pharmacopeia (JP), etc.). These standards are used by manufacturers to help ensure the products are of the appropriate chemical purity and quality, in the appropriate solution or compound, to ensure stability, safety, and efficacy.”

To determine whether a particular drug is available in a pharmaceutical-grade consult the FDA database. The Orange Book is the reference for FDA-approved human drugs, and the Green Book is the reference for FDA-approved veterinary drugs.

For all agents administered to animals, the following must be considered in the order presented for pharmaceuticals and reagents of all kinds prior to use:

1. FDA approved veterinary or human pharmaceutical compounds;
2. FDA approved veterinary or human pharmaceutical compounds used to compound a needed dosage form;
3. USP/NF, BP, or other pharmacopeia recognized pharmaceutical grade compounds used in a needed dosage form;
4. Analytical grade bulk chemical used to compound a needed dosage form (requires justification); and
5. Other grades and sources of compounds (requires justification).

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Pharmaceutical-grade drugs will have a National Drug Code (NDC) included on the packaging along with a lot number, expiration date, and other relevant details.

**III. UC Merced Policy:**

- Drugs are manufactured by a pharmaceutical producer under good manufacturing practices and approved by the FDA. Investigators are expected to use pharmaceutical-grade or veterinary-grade medications, including anesthetics, analgesics, and euthanasia agents, in research proposals whenever they are available, including acute procedures.
- When using nonpharmaceutical grade compounds, consideration should be given to the following:
  - Grade,
  - Purity,
  - Sterility,
  - pH,
  - Pyrogenicity,
  - Osmolality,
  - Stability,
  - Site/route of administration,
  - Formulation,
  - Compatibility,
  - Pharmacokinetics,
  - Animal welfare/Scientific issues related to toxicity, side effects, animal health and research results
- OLAW and the USDA understands the need for nonpharmaceutical grade compounds; nevertheless, they have determined nonpharmaceutical grade compounds use is based on (1) scientific necessity, (2) unavailability of acceptable veterinary or human pharmaceutical-grade compound, and (3) specific review and approval by the IACUC.
- Cost savings alone is an inadequate justification for nonpharmaceutical grade compounds
- Sterile, pyrogen-free materials and diluents must be used whenever possible. Materials may be sterilized by autoclaving or filtration (using a 0.22 $\mu$  filter) and endotoxin removed through an endotoxin filter; the latter is particularly important for injectables. Additionally, injectables should be physiologic (e.g., pH, osmolality). For oral administration, use food grade vehicles or diluents.
- PIs must indicate all nonpharmaceutical (e.g., chemical grade) agents used in the study and provide a justification for each, including diluents where applicable.
- Drug safety, efficacy, and shelf-life measures should be established to protect subject welfare and promote valid experimental outcomes.

The use of nonpharmaceutical-grade chemical compounds in experimental animals under certain circumstances has been, and will continue to be, a necessary and acceptable component of biomedical research. OLAW and the USDA have determined that their use should be based on scientific justification, and specific review and approval by the IACUC. Acceptable justifications include the following:

- An equivalent veterinary or human pharmaceutical-grade compound does not exist, or it is unavailable
- The equivalent veterinary or human pharmaceutical-grade compound is not available in the appropriate formulation or concentration required.

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- Although there is an equivalent veterinary or human drug available, the chemical grade is required to replicate methods from previous studies.
- The equivalent veterinary or human pharmaceutical-grade compound contains preservatives or inactive ingredients which may confound the research goals of the study.

**IV. References:**

- AAALAC—International (FAQ): Non-Pharmaceutical-Grade Compounds
- OLAW Position Statement #3
- OLAW Webinar: Use of Non-Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals
- USDA Policy #3
- NRC. 2011. *Guide for the Care and Use of Laboratory Animals*. National Academies Press, Washington, DC.

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OLAW Webinar Notes:

[AAALAC, slide 11]

It is also important for the IACUC to ascertain key quality control and assurance factors as follows:

- Provisions for drug reconstitution, preparation and/or compounding should be appropriate.
- Attention should be paid to drug purity, sterility, osmolality, concentration and other parameters impacting subject response and animal welfare.
- Drug safety, efficacy and shelf-life measures should be established to protect subject welfare and promote valid experimental outcomes.
- And personnel responsible for the preparation, administration and experimental evaluation of compounds at the institutional level should have adequate training, experience and performance.

[OLAW, slide 17]

In the animal study proposal, the investigator should identify any drugs, biologics or reagents that will be administered to animals. If these agents are not human or veterinary pharmaceutical-grade substances, the investigator must provide a scientific justification for their use and describe the methods that will be used to ensure appropriate preparation and administration.

[OLAW, slide 20]

Although an equivalent veterinary or human drug is available for experimental use, the chemical-grade reagent is required to replicate methods from previous studies because results are directly compared to those of replicated studies.

[OLAW, slide 37]

...this is similar to an IACUC approving a standard operating procedure for a surgical procedure, which then can be referenced by the PI in the protocol. So those approvals should be periodically reviewed by the IACUC at least every three years.

[Questions not answered during the webinar]

The following are important concepts for IACUCs and investigators considering the use of pharmaceutical- and non-pharmaceutical-grade substances in research with animals:

- Investigators must use pharmaceutical-grade substances in biomedical and behavioral research with animals when they are available. Non-pharmaceutical- grade substances may be used if justified by the researcher and approved by the IACUC.
- The use of non-pharmaceutical-grade substances has been, and will continue to be, a necessary and acceptable component of biomedical research.
- IACUCs, veterinarians, animal care personnel and investigators are responsible for ensuring that animals used in research, teaching, and testing are treated humanely.
- OLAW recognizes that investigators face many challenges and we fully support the essential work that they do. Ultimately, it is up to each IACUC, practicing local self- monitoring, to ensure that any pain and distress experienced by animals is avoided or minimized, while at the same time supporting justified scientific research.

[1. Question.]

How does one determine whether a particular drug is available in a pharmaceutical-grade? Is there one place to determine what the source(s) might be?

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Answer. You may determine what is available by consulting the FDA database. The Orange Book is the reference for FDA-approved human drugs. The Green Book is the reference for FDA-approved veterinary drugs.

[Question 11, Answered]

Drugs are manufactured by a pharmaceutical producer under good manufacturing practices and approved by the FDA.

[Question 12]

Some investigators use chemicals from SIGMA for various compounds (e.g., tribromoethanol) for anesthetics that are not made in a pharmaceutical grade. However these chemical bottles have no expiration date labeled. They appear to have a date of manufacture only. I do not know how long these chemicals can be expected to be "in date". Do you have any guidance on this?

Answer. If you cannot find information that you need about a product on a commercial website, contact the manufacturer. It would be reasonable for the IACUC to ask the investigator to provide information about stability of a compound prepared in the laboratory. OLAW Position Statement 3 states: "The IACUC is responsible for evaluating the potential adverse consequences of such agents when used for research. In making its evaluation, the IACUC may consider factors including, for example: grade, purity, sterility, acid-base balance, pyrogenicity, osmolality, stability, site and route of administration, compatibility of components, side effects and adverse reactions, storage and pharmacokinetics."