

	UCSD INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE POLICY MANUAL	POLICY # 31.03  Issued: 11.4.2005 Revised: 08.15.2012 Revised: 03.25.2019
	Use of Non-Pharmaceutical Grade Compounds in Animals	

### **I. Background and Purpose**

The University of California is committed to the improvement of human and animal health and the advancement of science. When these pursuits involve the administration of compounds to animals, UCSD is committed to their humane care and use as specified in the [Guide for the Care and Use of Laboratory Animals](#), the [PHS Policy](#) and the [Animal Welfare Act](#).

These regulations require that all compounds administered to animals be pharmaceutical grade if available. Non-pharmaceutical grade compounds with undefined or higher levels of impurities, as well as poorly formulated non-commercial preparations can introduce unwanted experimental variables or have toxic effects. The use of a pharmaceutical grade preparation ensures the compounds meet established standards of purity and composition, which may prevent adverse effects on animals or research outcomes.

### **II. Who Should Read This Policy**

All personnel on an approved IACUC protocol engaged in or responsible for administration of experimental and/or therapeutic compounds to animals.

### **III. Definitions**

<b>Term</b>	<b>Definition</b>
Pharmaceutical grade compound	Any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices (GMP) which is approved, conditionally approved, or indexed by the FDA or for which a chemical purity standard has been written or established by a recognized compendium (e.g., USP-NF, BP). 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.
USP/NF	United States Pharmacopeia/National Formulary
BP	British Pharmacopeia
FDA	Food and Drug Administration; FDA approved compounds are manufactured using USP/NF compounds
Non-availability	Not commercially available from an active US vendor; includes formulations supplied as tablet, capsule, injectable, etc.
Chemical Grade Compound	Compounds which may be chemically identical to their pharmaceutical grade counterparts, but do not conform to recognized standards for purity and bioavailability.

#### IV. Policy

1. Therapeutic Compounds for Clinical Use
  - For all species, when commercially available, therapeutic compounds (e.g., anesthetics, analgesics, antibiotics, euthanasia) and diluents must be pharmaceutical grade, even when used in acute procedures.
2. Experimental Compounds for Research Use
  - For USDA Covered Species, all compounds administered must be pharmaceutical grade whenever they are available, even in acute procedures.
  - For Non-USDA Covered Mammals and Birds, any substance or vehicle administered through a route other than oral (e.g., eating, drinking, gastric gavage) must be pharmaceutical grade if available and suitable for the proposed route of administration. Such routes include, but are not limited to injection, inhalation, topical application and irrigation (i.e. placed into surgical opening or wound).
  - For Fish and Amphibians, any substance or vehicle administered through a route other than immersion or oral ingestion (eating/drinking/gastric gavage) must be pharmaceutical grade if available and suitable for the proposed route of administration. Such routes include but are not limited to injection and irrigation (i.e. placed into surgical opening or wound).
3. Non-pharmaceutical grade chemical compounds, may only be used in animals after specific review and approval by the IACUC for reasons such as scientific necessity or non-availability of an acceptable veterinary or human pharmaceutical grade product. Cost savings alone are not an adequate justification for using non-pharmaceutical grade compounds in animals. The preparation, storage and use of any non-pharmaceutical grade compounds must be explicitly detailed in the IACUC protocol, and IACUC approval must be secured prior to use of the drug.
4. Prepared compounds must be labeled to include:
  - the name of the compound(s)
  - the concentration
  - the date the product was mixed
  - the expiration date of reconstituted compounds(s)
5. Documentation of appropriate methods used to prepare and handle experimental compounds, taking into account pharmaceutical criteria such as sterility, shelf-life, and storage conditions, must be available to inspectors. Assistance in finding acceptable alternatives to non-pharmaceutical grade compounds is available from the veterinary staff of the Animal Care Program.

#### V. Related Documents

UCSD Documents	<a href="#">Guidelines on the Use of Injectable Drugs in Animals</a> <a href="#">IACUC Policy 13 Euthanasia</a> <a href="#">IACUC Policy 34 Anesthesia</a> <a href="#">IACUC Policy 32 Expired Medical Materials</a> <a href="#">Anesthetic and Analgesic Dosages in Rodents and Rabbits</a> <a href="#">Guidelines for the Use of Avertin</a> <a href="#">Guidelines for the Use of MS-222</a> <a href="#">Guidelines for the Use of Urethane</a>
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Other Documents and References	<a href="#">Animal Welfare Act &amp; Regulations</a> <a href="#">The Guide for the Care and Use of Laboratory Animals</a> <a href="#">OLAW FAQ</a> <a href="#">AAALAC FAQ</a>
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## VI. Additional information

### 1. Understanding the difference between Therapeutic Compounds and Experimental Compounds

Therapeutic compounds (anesthetics, analgesics, euthanasia agents, antibiotics, etc.) almost always have pharmaceutical grade preparations available commercially. Federal mandates require the use of these pharmaceutical grade preparations. In the rare case that an appropriate therapeutic compound is not commercially available as pharmaceutical grade, the PI is responsible for preparing a sterile and physiologically-compatible preparation for use in animals. This preparation and storage must be described in the protocol and approved by the IACUC before use.

Experimental compounds (test compounds) sometimes do not have pharmaceutical grade preparations available commercially. The PI is responsible for preparing a sterile and physiologically-compatible preparation for use in animals. This preparation and storage must be described in the protocol and approved by the IACUC before use.

### 2. Best Practices for Reconstituting Non-Pharmaceutical Grade Compounds

If there is a scientific need to use a non-pharmaceutical grade compound and the UCSD IACUC has approved it in your protocol, the following guidelines should be followed:

- 1) Compounds must be sterilized prior to administration. The reconstituted compound may be sterilized by passing through a 0.2  $\mu\text{m}$  filter. Diluents and solvents used for reconstitution should be pharmaceutical grade if possible.
- 2) Reconstitution must be performed in an aseptic manner.
- 3) Reconstituted compounds must be labeled identifying the compound, the date of preparation and the expiration date.
- 4) Reconstituted compounds should be discarded before degradation occurs. If degradation period is unknown, prepare compound fresh for each use. A degraded compound is a compound that has failed to maintain its physical, chemical, therapeutic, microbiological and/or toxicological stability.
- 5) Follow all manufacturer guidelines and [UCSD's Guidelines on the Use of Injectable Drugs in Animals](#).

**Note:** pH of solutions for parenteral injection must be between pH 4.5 and 8.0. Use of a solution with a pH outside this range must be addressed in the animal use protocol. The osmolality of intravenously administered compounds should generally be formulated to a range matching the research species blood osmolality. Generally, agents with an osmolality greater than 600 mOsm/kg cause red blood cell crenation while agents less than 150 mOsm/kg will cause hemolysis, both of which are associated with pain and physiologic disturbances. Solutions with an osmolality less than 450 mOsm/kg are generally well tolerated by intravenous infusion in most research mammals.

### 3. Scientific Justification for Using a Non-Pharmaceutical Grade Compound

When a pharmaceutical grade preparation is available but cannot be used, the IACUC generally considers the following statements to be acceptable justification for the use of non-pharmaceutical grade compounds. Note: the IACUC may request additional information or documents in support of your justification.

- The pharmaceutical grade compound is not available in the appropriate concentration or formulation, or an equivalent vehicle control is not available.

Example wording used to provide acceptable justification:

“The pharmaceutical grade preparation of [compound name] is only available as an oral tablet. It is impractical to alter the tablets into an injectable formulation and the binders (specify compounds) used in the tablet are not suitable for intravenous injection. We would also be unable to recreate the identical vehicle for the control animals compromising the integrity of the data.”

- The pharmaceutical grade preparation contains unwanted fillers, diluents, vehicles and/or preservatives that will interfere with studying the effect of the active ingredient. (specify the specific compound(s) and indicate how it will interfere with the study.)

Suggested wording:

“The pharmaceutical grade preparation of [compound name] contains [unwanted compound name] which has been shown to affect [indicate effects] which would interfere with our ability to study the behavioral effects of [compound name].”

“Pharmaceutical grade [compound name] contains preservatives (specify) which has been known to interfere with the results of the histopathology.”

- A non-pharmaceutical grade compound is required to replicate methods from previous studies because the results are directly compared to the previous data.

Suggested wording:

“Although [compound name] is commercially available in pharmaceutical grade, a non-pharmaceutical-grade preparation has been used by the laboratory since [date]. The data collected on this protocol are part of a longitudinal study that depends on comparison of new data to results. The pharmaceutical grade preparation contains additional ingredients that may introduce new variables.”

- Available pharmaceutical grade compound is not appropriate for the specified route of administration (e.g., toxic vehicle, pH).

### 4. Chemical Compound Grades

If no equivalent veterinary or human drug is available for experimental use, then the highest grade equivalent chemical should be used and formulated aseptically and with a non-toxic vehicle as appropriate for the route of administration. When selecting compounds, the following order of choice should be applied:

- a. FDA approved veterinary or human pharmaceutical preparation;

- b. FDA approved veterinary or human pharmaceutical preparation used to compound a needed dosage form (dilute or combine with other preparations);
- c. USP/NF or BP pharmaceutical grade powder used to compound a needed dosage form (source and preparation must be described in protocol);
- d. Analytical grade bulk chemical used to compound a needed dosage form (source and preparation must be described in protocol);
- e. Other grades and sources of compounds (source and preparation must be described in protocol).

**Corresponds to official monograph (e.g. USP):** This USP purity grade indicates the compound was produced/procured, packaged and analyzed under appropriate quality systems for pharmaceutical applications according to the corresponding monograph. However, USP grade chemicals purchased from a chemical company are not FDA approved drug products.

**Meets analytical testing specifications:** These chemicals meet the latest testing specifications of the USP, NF, and/or FCC. For R&D and testing purposes only. These compounds are not intended for pharmaceutical use.

**Analytical Grade:** Generally applied to bulk chemicals, these products have a purity level of 99.9%. These may be used in animals with a certificate of analysis that documents the contaminants are less than 0.1% (for example: analytic grade ethanol may have up to 5% water or 5% benzene. Water is acceptable for animals; benzene is not). The critical parameters involved are absence of inhibitors such as traces of heavy metals as well as biochemical function tests for enzymes, coenzymes and enzyme substrates. Each requires a certificate of analysis for consideration in live animal use.

**Technical Grade:** These products are suitable for general industrial or non-critical tasks in the laboratory such as rinsing, dissolving or are used as raw materials in production tasks. These are chemicals that do not have an established standard set for quality and impurity levels or for products where the purity is <90%. Variation in color and physical form is possible.

**USP Reference Standards:** According to USP, Reference Standards are not for use in humans or animals as drugs or medical devices. They are intended for test and assay use only.

- **Primary Standards:** These are produced according to the national pharmacopeias, such as USP and BP.
- **Secondary Standards:** These are produced by other entities such as Sigma, a compounding pharmacy, or a pharmaceutical company. They test the quality and purity of secondary standards and compare results to primary standards.

**Reagent Grade:** Chemicals of sufficient purity for use in chemical analysis, chemical reactions or physical testing.

**Laboratory Grade:** A chemical with exact levels of impurities unknown; usually pure enough for educational applications, but not pure enough to be offered for food, drug, medicinal, or research use.

**Food Grade:** Products meet the strength specifications and maximum impurity limit indicated in the Food Chemicals Codex (FCC). Food grade is acceptable when used as a food or carrier product for orally consumed substances. Food grade is not acceptable for injection into a live animal. When formulating a compound for oral use, investigators should use food-grade materials if available.

**Investigational Substance/Drug:** Supplied by its manufacturer for testing in an experimental setting only. These substances generally do not have chemical purity standards established and are considered non-pharmaceutical grade.

## 5. Common Pharmaceutical Grade Diluents and Vehicles

- 0.9% Sodium Chloride for injection – multiple sources (e.g., MWI, Baxter Healthcare)
- Ethanol – multiple USP sources (FCC is intended for oral administration only) including:
  - [Spectrum Chemical](#)
- Tween 80 (Polysorbate) – NF grade can be found at:
  - [Spectrum Chemical](#)
- Propylene Glycol – USP grade can be found at:
  - [Spectrum Chemical](#)
- Mineral oil – USP grade found in most drug stores (e.g., Walgreens, CVS) and at Spectrum Chemical
- Corn oil – USP grade can be found at:
  - [Spectrum Chemical](#)
  - [WHC Co, Inc.](#) (also includes other USP-grade oils)
  - [Parchem](#)
- DMSO (Dimethyl Sulfoxide) – USP grade can be found at:
  - [Spectrum Chemical](#)
  - [Gaylord Chemical](#)
  - [Fagron](#)

## 6. Frequently Asked Questions

### How do I know if a compound is pharmaceutical grade?

If a drug or compound is used in people or animals there is usually a pharmaceutical grade preparation available. These preparations are made under GMP (Good Manufacturing Practices) by a pharmaceutical company (e.g., Eli Lilly, Pfizer, Hospira) and are acquired from human and veterinary medical supply companies and often require a prescription. You will usually see 'USP' on the label or "Approved by the FDA" with an FDA code such as NDA, ANDA, or ANADA (or NDC if FDA registered) followed by a number.

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), inactive ingredients, and biologics such as allergenics, cellular and gene therapy products, blood products and vaccines.

Powders and other compounds purchased from chemical storehouses (e.g. Sigma) are not considered pharmaceutical grade. The bottles will usually be labeled with a disclaimer such as, "For laboratory use only. Not for drug, household or other uses."

FDA approved human drugs (Orange Book):

<https://www.fda.gov/drugs/informationondrugs/ucm129662.htm>

FDA approved veterinary drugs (Green Book): <https://animaldrugstfda.fda.gov/adafda/views/#/search>

Inactive ingredients: <https://www.fda.gov/Drugs/InformationOnDrugs/ucm080123.htm>

Biologics: <https://www.fda.gov/BiologicsBloodVaccines/ucm133672.htm>



Figure 1. Non-pharmaceutical grade Dopamine



Figure 2. Pharmaceutical grade Dopamine

### I have a USP grade powder. Is the compound considered pharmaceutical grade?

It depends. If the compound is supplied in a sterile lyophilized bottle intended for injection, for example an antibiotic such as Cefazolin (figure 3.), it is considered a pharmaceutical grade preparation. Instructions on how to properly reconstitute the drug for injection will be found on the label. As long as the manufacturer's instructions are followed (e.g. correct sterile diluent is used), the drug's preparation does not need to be described in the IACUC protocol as it is considered pharmaceutical grade.



Figure 3. Pharmaceutical grade Cefazolin for Injection



Figure 4. USP purity grade Amoxicillin, considered non-pharmaceutical grade. Parenteral administration requires justification.

If the compound is supplied in a screw, flip-top or other non-aseptic container (figure 4.), it is not considered a pharmaceutical grade preparation. Even if you are using a 'USP' or 'Pharma grade' powder, which is what pharmaceutical companies use to make the final preparation, it will not be considered pharmaceutical grade since the final preparation is made in your lab. Since the way the compound is prepared affects the sterility, effectiveness and safety of the drug, its preparation would need to be described on the protocol and assessed by the IACUC.

**Is there a pharmaceutical grade preparation of MS-222?**

Yes. Pharmaceutical grade MS-222 is available under the trade name Tricaine-S. It is manufactured by Syndel (formerly Western Chemical, Inc) but is available from a variety of vendors.

[Tricaine-S from Syndel](#)**What is parenteral administration?**

Parenteral refers to the administration of substances through any non-oral means. Parenteral articles must adhere to stringent standards designed to meet USP requirements for sterility, pyrogens, particulate matter and other contaminants, and where appropriate, contain inhibitors of the growth of microorganisms.

**What are particulates?**

Particulates consist of extraneous mobile undissolved particles unintentionally present in the solution. Particulates testing is of particular concern in injections and parenteral infusions. Water designated for use in injectable products requires this testing to ensure particulate matter will not be introduced into the animal. Pharmaceutical grade diluents that are formulated for injection, such as water for injection, have been tested by the manufacturer.

**What are pyrogens?**

Pyrogens, such as bacterial endotoxins, have been known to cause fever or physiological shock when injected into an animal. Pharmaceutical grade compounds are tested for pyrogens. Filtering of a non-pharmaceutical grade compound does not remove pyrogens, and sterility does not assure that pyrogens are not present.

**What is the difference between water for irrigation and water for injection?**

Sterile water for injection (WFI) is the highest purity water available and is intended to be used parenterally. Water for injection is tested for bacterial endotoxins and particulates.

Sterile water for irrigation is not tested for particulates and is not suitable to be used as a diluent or be injected into animals.

**What is the difference between PBS and saline?**

0.9% Sodium Chloride (NaCl) for injection, also referred to as normal saline or physiological saline, is a sterile solution containing water for injection and sodium chloride salt to render it isotonic and is suitable for parenteral administration.

PBS, or Phosphate Buffered Saline, is a laboratory grade buffer solution containing water, sodium chloride (NaCl) and sodium phosphate (Na<sub>2</sub>HPO<sub>4</sub>). In some instances, potassium, or even calcium or magnesium may be added to the solution. PBS is not pharmaceutical grade. *Note: Some preparations may be available for purchase that utilize USP grade ingredients, but the final product is not considered pharmaceutical grade.*

Commercial preparations of PBS are not typically tested for pyrogens or particulates and the solution is not intended for injection. If PBS must be used as a diluent or vehicle, careful attention must be made to the pH, tonicity and osmolality of the solution. Methods for addressing sterility, removal of particulates, and pyrogens should be described on the protocol.

**May I use purified or distilled water to inject drugs into animals?**

Distilled Water, Deionized Water, Purified Water, Filtered Water, and High-Purity Water are commonly used in laboratories as solvents for reagent preparation, in various analytical applications or test apparatus cleaning, and for the preparation of non-parenteral compendial dosage forms. Water quality testing for these grades vary and generally do not include particulate testing and thus, are not intended for injection.

**What is an excipient?**

Excipients are often referred to as 'inactive ingredients'. They are comprised of everything except the active pharmaceutical ingredients (APIs). Excipients are usually chosen because of their ability to stabilize or maintain the bioavailability of the API or to ensure the solution will not cause pain or damage tissue upon injection.

**What is tonicity and why is it important?**

Solutions should be made isotonic to avoid crenation or hemolysis of red blood cells and to prevent pain and discomfort if solutions are injected. This requires the osmotic pressure of solutions to be approximately the same as that in the blood or tissue.

Solutions of sodium chloride, dextrose, and Lactated Ringers are common examples of pharmaceutical preparations that contain tonicity agents. Tonicity agents may be present as ionic and/or nonionic types. Examples of ionic tonicity agents are alkali metal or earth metal halides such as CaCl<sub>2</sub>, KBr, KCl, LiCl, NaI, NaBr or NaCl, Na<sub>2</sub>SO<sub>4</sub>, or boric acid. Nonionic tonicity agents include glycerol, sorbitol, mannitol, propylene glycol, or dextrose.

**I obtained a compound from an academic collaborator. Do I still need to describe its preparation in the IACUC protocol?**

The preparation of all non-pharmaceutical grade compounds needs to be described in Question 17B and 17C, as appropriate. If the compound will be prepared in another lab or institution, the methods used to prepare the drug still need to be described and approved by the IACUC.

**If I have more questions or need assistance, whom can I contact for help?**

If you have any questions, please email the IACUC Office at [iacuc@ucsd.edu](mailto:iacuc@ucsd.edu). If you need assistance in obtaining a pharmaceutical grade preparation, please email the ACP Veterinarians at [acp-veterinarians@ad.ucsd.edu](mailto:acp-veterinarians@ad.ucsd.edu).