

## **IACUC Policy**

# **Non-pharmaceutical Grade Substances and Compounds, Use of**

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### **Policy**

#### **Use of non-pharmaceutical grade compounds at SDSU**

1. Investigators must use pharmaceutical grade compounds whenever they are available, even in acute procedures.
2. 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 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. Justification must be provided in APF supplement 4.
3. Prepared compounds must be labeled to include the name of the medication, the date the product is mixed, expiration date of reconstituted compounds(s), final concentration and diluent. 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. See Formulation of Non-pharmaceutical Grade Compounds page 4.

### **Definitions**

Pharmaceutical Grade Compound: Any compound (drug, biologic, reagent, diluent, etc.) which is approved by the Food and Drug Administration (FDA), manufactured in compliance with the FDA Good Manufacturing Practices (GMP) guidelines and for which a chemical purity standard has been written/established by United States Pharmacopeia/National Formulary (USP/NF) or British Pharmacopeia (BP). (7)

Non-pharmaceutical Grade Compound: Chemicals or compounds which are not specifically designed for medical use to include pure chemicals obtained from Sigma or a similar company (10).

Expiration Date: The date printed on the label or package by the manufacturer for products specifically designed for medical use including pharmaceutical grade compounds. Preservative free containers or formulations should be discarded within 1-7days from first use.<sup>[rs1]</sup> Working solutions of anesthetics must be used within 3 weeks of solution preparation. All solutions used in animals should be used within 30 days after preparation of the compound. For further information about the determining Expiration Date or the possible use of expired materials see the Expired Materials in Animals, Use of IACUC Policy.

### **Introduction**

In the course of their research, investigators may have questions pertaining to the use of non-pharmaceutical grade compounds in research animals. The SDSU IACUC policy on this issue incorporates guidance from the NIH Office of Laboratory Animal Welfare (OLAW), the USDA Animal Care Division and AAALAC, International. These materials, as well as policies from a number of other institutions are referenced at the end of this document.

### **Non-Pharmaceutical Grade Compounds**

Investigators are expected to use pharmaceutical grade compounds whenever possible. However, the use of non-pharmaceutical grade compounds in experimental animals may be necessary in the conduct of biomedical research under certain circumstances. The testing of an investigational new drug or the non-availability of an acceptable human or veterinary pharmaceutical grade product, are situations which may necessitate the use of a non-pharmaceutical grade compound. A detailed description of the rationale and use of non-pharmaceutical grade compounds must be included in the IACUC protocol and IACUC approval must be secured prior to the use of the compound.

### **Applicable Guidance**

The following paragraphs are excerpted from OLAW Position Statement 3) Non-Pharmaceutical-Grade Substances (3), unless otherwise referenced:

OLAW and USDA agree that pharmaceutical-grade chemicals and other substances, when available, must be used to avoid toxicity or side effects that threaten the health and welfare of vertebrate animals and/or interfere with the interpretation of research results. However, it is frequently necessary to use investigational compounds, veterinarian or pharmacy compounded drugs and/or schedule I controlled substances to meet scientific and research goals. 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: 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.

Investigators and IACUCs should consider relevant animal welfare and scientific issues including safety, efficacy, availability of pharmaceutical grade compounds, and the inadvertent introduction of new variables. **Cost saving alone is not an adequate justification for the use of non-pharmaceutical grade or compounded drugs 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 (1)

Although the potential animal welfare consequences of complications are less evident in non-survival studies, the scientific issues remain the same. The principles and need for professional judgment outlined above apply to non-survival studies. Procedures that may cause more than momentary or slight pain or distress to the animals must be performed with sedation, analgesia, or anesthesia agents using veterinary or human pharmaceutical-grade compounds, unless the use of an investigational compound or formula is scientifically necessary, appropriately justified, and approved by the IACUC. The use of a non-pharmaceutical grade euthanasia agent must meet the same standards.

OLAW's guidance on the use of non-pharmaceutical grade substances was first published in 2003 (ref) and posted on the OLAW website in 2006. The USDA's position on non-pharmaceutical grade substances may be found in Policy 3 of the Animal Care Manual (1). In addition, OLAW, with USDA and AAALAC, offered additional guidance through a webinar on the "Use of Non-Pharmaceutical Grade Chemicals and Other Compounds in Research with Animals" (4).

AAALAC distinguishes between clinical and research use of non-pharmaceutical grade compounds in their FAQ's (2). Research use is defined as compounds used to accomplish the scientific aims of the study. If available, and suitable, pharmaceutical-grade compounds are preferred; but when non-pharmaceutical grade preparations are used, AAALAC International will expect investigators and the IACUC to consider the following factors:

- Use must be compliant with applicable national or regional regulatory guidelines and requirements and the requirements of relevant funding agencies.
- A scientific justification is provided.
- The pharmaceutical grade compound is not available in the appropriate concentration or formulation or the appropriate vehicle control is unavailable.
- The compound is required to generate data that are part of an ongoing study or that are comparable to previous work.
- The chemical properties of the compound are appropriate for the study and the route of administration (e.g., the purity, grade, stability in and out of solution, solution vehicle properties, pH, osmolality, pyrogenicity and compatibility of the solvent and other components of final preparation). In some cases the reagent-grade of the compound may be as or more pure than the pharmaceutical grade.
- The method of preparation, labeling (i.e., preparation and use-by dates), administration and storage of formulations should be appropriately considered

with the aim of maintaining their sterility and quality (i.e., to prevent inadvertent co-administration of infectious agents or contaminants).

### **Rationale for Use of Non-pharmaceutical Grade Compounds**

Acceptable considerations for the use of non-pharmaceutical grade compounds are as follows (6):

- No equivalent veterinary or human drug is available for experimental use. The highest grade equivalent chemical reagent is to be used and formulated aseptically, with a non-toxic vehicle, as appropriate for the route of administration. USP, NF or BP grade should be used if available and passed through a sterile 0.2 micron filter.
- Although an equivalent veterinary or human drug is available for experimental use, the chemical grade reagent might be required to replicate methods from previous studies if it is the only option to produce results that are directly comparable.
- Although an equivalent veterinary or human drug is available, dilution or change in formulation is required.
  - If the formulation as provided must be diluted, altered by addition, or otherwise changed, there may be no advantage to be gained by using the USP formulation.
  - In this situation, use of the highest grade reagent may have the advantage of single-stage formulation and also result in purity that is equal to or higher than the human or veterinary drug.
  - Professional judgment should be used to determine the appropriate test material and to ensure use of an agent with the least likelihood for causing adverse effects.
- The available human or veterinary drug is not concentrated enough to meet experimental requirements.
- The available human or veterinary drug does not meet the non-toxic vehicle requirements for the route of administration.

### **Formulation of Non-pharmaceutical Grade Compounds**

Formulations should be compounded according to methods of successful use/efficacy in published scientific literature. Dilutions or mixtures of compounds must be prepared using sterile technique. Whenever possible, use pharmaceutical grade and/or sterile components (e.g., diluents, solvents, vehicles, additives) in the formulation. It is recommended to pass solutions through a filter (2µm or finer) at the time of preparation or passage to a storage container. Measures should be taken to ensure physiologic compatibility (pH, pyrogenicity). Prepared compounds must be stored properly (e.g. proper temperature, light levels) and in a manner which maintains sterility. The label should include the following information: name of the compound(s), final concentration, diluent (if applicable), date of preparation, and date of expiration.

## Use of Expired Drugs and Materials

The use of expired medical materials such as drugs, fluids, or sutures on animals is not considered to be acceptable veterinary practice and does not constitute adequate veterinary care as required by current animal care and use regulations. Medical materials, such as catheters, gloves, or sutures, are often imprinted with an expiration date, beyond which the manufacturer does not guarantee the safety or stability of the item. However, in some instances there may be a rationale for utilizing expired materials such as an instance where the efficacy and safety of the product(s) in question can be assured past the expiration date and the item(s) are difficult to replace. For more information about determining expiration date of a material, see the SDSU IACUC Policy for the Use of Expired Materials in Animals.

## Proper Disposal Procedures

The SDSU EHS has established the following procedures for disposal of unwanted or expired pharmaceutical and non-pharmaceutical grade therapeutics i.e. anesthetics, analgesics, euthanasia agents, antibiotics, etc. including experimental compounds, i.e. test compounds:

**Note: Unwanted or expired pharmaceutical and non-pharmaceutical therapeutics including experimental compounds must never be disposed in biohazardous red bags or sharps wastes container.**

- For unwanted or expired controlled therapeutics or experimental compounds (including diluted or reconstituted controlled substances):
  1. Contact the Controlled Substance Program Manager at x42865 or [mmtran@mail.sdsu.edu](mailto:mmtran@mail.sdsu.edu) to schedule an appointment to surrender and transfer custody of the controlled substances to EHS for proper disposal.
  2. Complete and submit the Controlled Substance Surrender Record form.
  3. Surrender unwanted and expired controlled substances including empty containers and completed Dispense Record of the controlled substance.
- For unwanted or expired non-controlled therapeutics or experimental compounds:
  1. Contact EHS at x46778 and request for waste pick up of expired non-controlled therapeutics or experimental compounds.

## Possible Exception to this Policy (Must be justified and approved by the IACUC)

**PENTOBARBITAL:** Pentobarbital has a long history of effective use, especially in rodents or small mammal species. In recent years, the medication has fallen out of favor with human healthcare use and consequently, most producers have ceased producing or selling pentobarbital as an injectable pharmaceutical grade product (currently there is only one company producing Nembutal). Current costs for pharmaceutical grade pentobarbital exceeds \$1000.00 per 50 ml bottle. Availability has also declined as one provider exercises a monopoly on the sales and distribution of this agent. While most researchers are able to convert to alternative medications, for certain applications and

certain studies, scientific necessity requires continued use of this barbiturate.

The NIH has stated that 'The exorbitant cost of this product has placed it logistically into the unavailable category. Regulatory guidance on this matter specifically allows for use of non-pharmaceutical-grade compounds due to non-availability and with IACUC approval. Therefore, the IACUC will consider and may approve requests to use a non-pharmaceutical grade of pentobarbital under the following circumstances.

**Note: With this said, pharmaceutical grade pentobarbital is available exclusively for euthanasia at an affordable, much lower cost through various vendors, trade names Euthasol, Fatal-Plus, Sleepaway If you choose to use the non-pharmaceutical grade for euthanasia, it must be further justified and approved by the IACUC.**

The preparation and use of this anesthetic must be:

- Scientifically necessary,
- Appropriately justified,
- Prepared from a reagent or analytical-grade powder; properly prepared by your pharmacist or other knowledgeable individual (e.g., chemist, veterinarian, researcher), with assurance of appropriate storage and handling, and
- Approval by the IACUC. In making its decision the IACUC must consider the side effects, stability, storage requirements and other considerations associated with the preparation of this agent (the PI must provide this information for IACUC consideration).

#### **Example of Recipe for 60 mg/ml Sodium Pentobarbital stock solution**

##### **a. INGREDIENTS**

- 6 grams sodium pentobarbital
- 10 ml ethanol (95%) USP
- 40 ml propylene glycol USP
- 0.9% saline USP

##### **b. STEPS:**

- Dissolve the pentobarbital powder in the ethanol.
- Add 25 ml of saline (but only after the pentobarbital is completely dissolved), mix thoroughly.
- Add 40 ml propylene glycol, mix.
- Bring to final volume (100 ml) with 0.9% saline.

#### **NOTES:**

1. The pentobarbital concentration in the final solution is 60 mg/ml.
2. Stock solutions must be protected from light and maintained at 4°C for no longer than 6 months.
3. Stock solutions must be passed through a sterile 0.2 micron filter prior to being stored.
4. Stock solutions must be prepared and stored in sterile containers.

5. Please see the IACUC Policy on Use of Non- Pharmaceutical-Grade Chemicals and Compounds for guidance on filtration and preparation.
6. Working solutions can be prepared and maintained similar to stock solutions, but can be stored at room temperature for up to 30 days.
7. Transfer of solutions must utilize sterile supplies and techniques.
8. All containers must be labeled with material name, concentration, date prepared, storage requirements, expiration date, and the initials of the person making the solution.
9. Use must be recorded similar to other controlled substances.
10. Standard procedures for monitoring plane of anesthesia apply and supplemental dosing is to be given as needed.
11. Prior to removal or transfer of any medication from a vial, swab rubber port of the vial with alcohol and allow the port to dry completely.
12. **Labeling** – If a drug is removed from its original packaging a label **MUST** be placed on the new container. Please list the name of the drug, the concentration of the drug and the beyond use date.
13. Commercial instruments are available for measuring pH and osmolality.
14. Do not administer non-sterile solutions, outdated solutions, more concentrated solutions, or higher doses than recommended above.

#### References:

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2. AAALAC Frequently asked questions about Non-Pharmaceutical Grade Compounds  
[http://www.aaalac.org/accreditation/faq\\_landing.cfm#B9](http://www.aaalac.org/accreditation/faq_landing.cfm#B9)
3. OLAW Position Statement- Non-Pharmaceutical Grade Substances
4. Transcript of OLAW On-line Seminar broadcast on March 1, 2012 - Use of Non-Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals
5. OLAW Frequently Asked Questions-Use of expired pharmaceuticals, biologics, and supplies in animals.  
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<http://ncifrederick.cancer.gov/lasp/acuc/frederick/Media/Documents/ACUC48.pdf>
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9. UCSD Policy on the Use of Non-Pharmaceutical Grade Compounds in Animals, Rev 8/5/2012  
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<http://www.upenn.edu/regulatoryaffairs/Documents/iacuc/guidelines/iacucguideline-expireddrugs.pdf>
13. Duke University IACUC Policy Use of Pharmaceutical and Non-pharmaceutical Grade Substances in Animals Rev 05-28-2015