Institutional Animal Care and Use Committee

Policy on Non-Pharmaceutical Grade Compounds

Date Reviewed: 12/11/19

I. Purpose

This policy establishes standards of review for the IACUC to ensure animal welfare is preserved. The use of non-pharmaceutical grade compounds can present a risk to animal welfare due to concerns over consistency, contamination, or preparation. This policy has been developed to ensure that UCSC complies with the Guide for the Care and Use of Animals, 8th Edition, and the NIH Guidelines for the Use of Non-Pharmaceutical Grade Compounds in Laboratory Animals and the Animal Welfare Act and Regulations.

II. Regulatory or Accreditation Authority

USDA Animal Care Resource Guide, Policy #3. March, 2014. - Non- pharmaceutical-grade substances should only be used in regulated animals after specific review and approval by the IACUC.

Guide for the Care and Use of Animals, Eighth Edition, p. 31. November, 2013. - 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 (USDA 1997b). The use of non-pharmaceutical-grade chemicals or substances should be described and justified in the animal use protocol and be approved by the IACUC

III. Scope

This policy applies to all animals cared for at UCSC, both in and outside of centralized vivarium.

IV. Definitions

Pharmaceutical Grade Compound: 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). According to guidance from the FDA, pharmaceutical secondary standards are acceptable for use in clinical animal studies if obtained from a reputable source and comply with compendia standards. A listing of pharmaceutical-grade drugs and biologics is available through 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.

V. Policy Requirements

Investigators are expected to use pharmaceutical-grade compounds whenever they are available, even in non-survival procedures.

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

- Scientific necessity;
- Non-availability of an acceptable veterinary or human pharmaceutical-grade compound;
- Non-availability of an acceptable alternative pharmaceutical-grade compound;
- Specific review and approval by the IACUC; and
- Appropriate 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.

Preparation of Sterile Non-Pharmaceutical Grade Compounds

No reagent-grade chemicals may be used in research animals if a pharmaceutical-grade compound is available through human or veterinary suppliers. Examples of available pharmaceutical-grade compounds frequently used in research animals include (but are not limited to): ketamine, xylazine, diazepam, buprenorphine, cefazolin, isoflurane and (sometimes) pentobarbital. Cost savings alone do not justify the use of non-pharmaceutical grade compounds in animals.

Terminal procedures under anesthesia may be considered for exception to these guidelines with approval from the IACUC.

If a pharmaceutical-grade compound is not available through human or veterinary suppliers, the Principal Investigator or their staff may compound the drug in their laboratory.

Examples of compounds not always available through suppliers include (but are not limited to): experimental test compounds and (sometimes) pentobarbital. If the drug is to be compounded the following procedures must be followed to insure sterility of the final product:

- All manipulations must occur in sterile vessels using sterile instruments (spatulas, syringes/needles, dosing vials, etc.…). Work should be carried out in a biosafety cabinet or chemical fume hood to reduce contamination of the area.
- The drug must be reconstituted with sterile diluents (e.g., water, Phosphate Buffered Saline, DMSO, ethanol, oil) prepared by filtration through a 0.2 micron filter or by autoclaving according to the instructions provided by the manufacturer of the reagent-grade chemical.
- The final solution should be adjusted so that it has a pH value of between 4 and 9.5.
- After thorough mixing, the solution must be filtered into a sterile vial through a 0.2 micron filter to ensure removal of bacteria and other contaminants.
- The vial must be labeled with the drug name, concentration of the solution, the date of compounding and the expiration date (maximum of six months from the date of compounding).
- The solution must be handled in a manner to ensure continued sterility of the contents.

- The expiration date of the compounded solution is six months from the date of compounding at a maximum. Any solution remaining after six months must be discarded and not used in laboratory animals.
- Regardless of age, solutions should be discarded if changes in color and/or precipitation occur.

Appendices for the Use of Non-Pharmaceutical Grade Compounds

Appendices are provided as IACUC suggestions or recommendations. Deviation from the attached appendices may require IACUC approval.

Appendix A: Guidelines for Selection of Compounds for Use in Research IACUC

When selecting compounds, the following order of choice should be applied: (This order of preference from the NIH Office of Animal Care and Use (OACU), Animal Research Advisory Committee (ARAC) guideline, "Guidelines for the Use of Non-Pharmaceutical Grade Compounds in Laboratory Animals.")

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 compound 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 used to compound a needed dosage form (requires justification);
5. Other grades and sources of compounds (requires justification).

Appendix B: IACUC 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 in its decision whether or not to approve the use of the substance:

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

Appendix C: Guidelines for Commonly Used Compounds IACUC

1. Pentobarbital sodium

Recent exorbitant cost increases of pentobarbital have placed it 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.

The following is the formulation of the commercially available pentobarbital solution: NEMBUTAL Sodium Solution (pentobarbital sodium injection, USP) is available in the following sizes: 20-mL multiple-dose vial, 1 g per vial (NDC 67386-501-52); and 50-mL multiple-dose vial, 2.5 g per vial (NDC 67386-501-55).

Each mL contains:

Pentobarbital Sodium, derivative of barbituric acid 50 mg

Propylene glycol % v/v

Alcohol 10%

Water for Injection qs

(pH adjusted to approximately 9.5 with hydrochloric acid and/or sodium hydroxide.)

The following is a scaled down formulation for the typical concentration and volume used in the vivarium based on the above formula:

To make 20 ml of a 48 mg/kg Pentobarbital solution:

0.96 g of sodium pentobarbital (Sigma P3761) 2 ml ethanol

8 ml propylene glycol qs Sterile water to 20 ml

Adjust pH to between 4 and 9.5 with hydrochloric acid and/or sodium hydroxide

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.

a. The preparation and use of tribromoethanol for survival surgery must be scientifically necessary, appropriately justified and approved by the IACUC.

i. Justification for using tribromoethanol should take into account the availability of commercially available pharmaceutical-grade alternatives, such as ketamine, xylazine, or isoflurane, and include a rationale for why these alternatives cannot be used.
ii. Tribromoethanol is not controlled by the Drug Enforcement Administration (DEA); justification solely based on this fact, however, is not considered scientific or adequate.
iii. Cost or convenience is not a scientific or adequate justification for the use of tribromoethanol.

b. If tribromoethanol will be used for anesthesia, it must be properly prepared and stored in accordance with the IACUC Avertin Formulary.
c. See the IACUC Guidelines on Preparation and Recipe for Avertin.

3. Tricaine methanesulfonate (TMS, MS-222®, Tricaine®-S, Finquel®)

a. 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.
b. See the UCSC IACUC SOP for MS-222.

Appendix D: Guidelines for New Investigational Compounds IACUC

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.

Appendix E: Additional References

a. NIH Office of Animal Care and USE, Guidelines for the Use of Non-Pharmaceutical Grade Compounds in Laboratory Animals (Last Revised, 2013) (http://oacu.od.nih.gov/ARAC/documents/Pharmaceutical_Compounds.pdf) (Last Visited, 2013).
b. OLAW Position Statement 3) Non-Pharmaceutical-Grade Substances (http://grants.nih.gov/grants/olaw/positionstatement_guide.htm#nonpharma) (Last Visited, 2013)
c. United Stats Pharmacopeia-National Formulary(USP- NF)(http://www.uspnf.com/uspnf/login)
d. British Pharmacopeia (BP) (http://www.pharmacopoeia.co.uk/)
e. FDA Drug Approval Database (http://www.fda.gov/Drugs/InformationOnDrugs/default.htm)