USE OF NON-PHARMACEUTICAL GRADE COMPOUNDS IN RESEARCH ANIMALS

1. PURPOSE

1.1. The purpose of this animal care and use protocol (ACUP) is to provide guidelines for the use of non-pharmaceutical grade compounds in research animals. This ACUP is intended for use by principal investigators and their staff. This ACUP is approved by the Cornell Institutional Animal Care and Use Committee (IACUC). Any deviation must be approved by the IACUC prior to its application.

2. SCOPE

2.1. This document applies to all qualified personnel administering compounds to research animals at Cornell University.

3. INTRODUCTION

3.1. The use of pharmaceutical grade compounds administered to research animals ensures that the compounds meet established documentable standards of purity, activity, and composition while safeguarding animal wellbeing and reproducible experimental outcomes. A pharmaceutical grade compound should be used when available. Administration of non-pharmaceutical grade compounds to animals must be scientifically justified and approved by the IACUC. Contact the Center for Animal Resources and Education (CARE) at Cornell University by emailing care@cornell.edu for more information or for assistance.

3.2. 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 Pharmacopoeia (BP).

4. MATERIALS AND EQUIPMENT

4.1. IACUC approved animal use protocol
5. PROCEDURE

5.1. Pharmaceutical Grade Compounds

5.1.1. Define within the applicable animal use protocol whether or not all compounds being administered to research and teaching animals are pharmaceutical grade.

5.1.2. Search FDA databases to determine if compounds are pharmaceutical grade.

5.1.2.1. The “Orange Book” is a reference for FDA-approved human drugs.

5.1.2.2. The “Green Book” is a reference for FDA-approved veterinary drugs.

5.1.2.3. Pharmaceutical grade compounds occasionally may not be listed in the Orange or Green book. These compounds should be labeled with a New Animal Drug Application / Abbreviated New Animal Drug Application (NADA / ANADA) or with a National Drug Code (NDC).

5.1.3. Cornell’s IACUC considers dilutions and or mixtures of compounds to be equivalent to pharmaceutical grade so long as all ingredients within the solution/mixture are pharmaceutical grade.

5.1.3.1. Safety considerations regarding sterility and proper storage must be considered (See Appendices).

5.1.3.2. Expiration of pharmaceutical grade mixtures are considered expired three months from date of preparation OR the date of the earliest expiration of an ingredient, whichever date comes first.

NOTE: The standard ketamine / xylazine rodent anesthesia solution has been established to be stable and effective for at least 6 months (BJ Taylor, et al.). As such, a sterile solution of this mixture can be maintained and used for up to 6 month following preparation so long as this does not exceed the expiration date of either the ketamine or the xylazine used to make the mixture.

5.1.3.3. All dilutions must be labeled minimally with:

5.1.3.3.1. Active compounds
5.1.3.3.2. Concentration
5.1.3.3.3. Preparation date
5.1.3.3.4. Expiration date
5.1.3.3.5. Individual who prepared mixture

NOTE: Contact CARE at care@cornell.edu for questions or concerns regarding the pharmaceutical status of animal use compounds.
5.2. Non-pharmaceutical Grade Compounds

5.2.1. The use of non-pharmaceutical grade compounds in animals must be described and justified in an animal use protocol and approved by the IACUC.

NOTE: Cost savings alone is not an acceptable justification.

5.2.2. See Appendices for examples of acceptable, unacceptable, and suggested wording for scientific justification of the use of non-pharmaceutical grade compounds.

5.2.3. Take precautions to ensure a reasonable degree of safety when preparing and using a non-pharmaceutical grade compound in regards to:

5.2.3.1. Grade
5.2.3.2. Purity
5.2.3.3. Sterility
5.2.3.4. pH
5.2.3.5. Pyrogenicity
5.2.3.6. Osmolality
5.2.3.7. Stability
5.2.3.8. Site / route of administration
5.2.3.9. Compatibility of components
5.2.3.10. Adverse reactions
5.2.3.11. Pharmacokinetics
5.2.3.12. Storage of drug (See Appendices)

6. PERSONNEL SAFETY

6.1. Medical Emergencies: CALL 911.

6.2. When working with animals wear appropriate PPE, observe proper hygiene, and be aware of allergy, zoonosis, and injury risks. Refer to the CARE Occupational Health and Safety webpage for more information.

7. ANIMAL RELATED CONTINGENCIES

7.1. Non-emergency veterinary questions and requests for care, email CARE veterinary staff at care@cornell.edu.

7.2. Emergency veterinary care is available at all times including after working hours and on weekends and holidays by calling the CARE pager (1-800-329-2456).

8. REFERENCES

8.1. FDA Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

8.2. FDA Green Book, Animal Drugs:
https://animaldrugsatfda.fda.gov/adafda/views/#!/search OLAW, FAQs, PHS Policy on Humane Care and Use of Laboratory Animals:
http://grants.nih.gov/grants/olaw/faqs.htm


### 9. APPENDIX

<table>
<thead>
<tr>
<th>A Guide to Justification of the Use of Non-Pharmaceutical Grade Compounds</th>
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<tbody>
<tr>
<td><strong>Justification that is typically acceptable:</strong></td>
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<tr>
<td>- Pharmaceutical grade not available from a veterinary or medical supplier</td>
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<td>- Pharmaceutical grade not available from a veterinary or medical supplier in the needed concentration</td>
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<tr>
<td>- Pharmaceutical grade contains unwanted fillers/diluents/vehicles/preservatives</td>
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<td>- Non-pharmaceutical grade compound required to replicate methods from previous studies because the results are directly compared to the previous data</td>
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<td>- Pharmaceutical grade compounds have known unwanted effects on measured outcomes substantiated by data or published reports</td>
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<td>- Available pharmaceutical grade compound is not appropriate for the specified route of administration (e.g. toxic vehicle, pH)</td>
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<td><strong>Inadequate justification:</strong></td>
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<td>- Cost savings alone</td>
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<td>- Administrative burden of acquiring and maintaining a DEA license</td>
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<td>- Consideration/elimination of only one of multiple pharmaceutical-grade alternatives</td>
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<td><strong>Suggested wording used to provide acceptable justifications:</strong></td>
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<tr>
<td>- &quot;[Compound name] is experimental in nature and no pharmaceutical-grade alternative is available. It is not practical or possible to generate a pharmaceutical-grade version of this novel compound.&quot;</td>
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<tr>
<td>- &quot;The commercially available pharmaceutical-grade form of [compound name] is not available in an appropriate concentration to meet the scientific requirements of this study, and it is not practical to alter the concentration to a useable formulation.&quot;</td>
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<tr>
<td>- &quot;Though [compound name] is commercially available in pharmaceutical grade, a nonpharmaceutical-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 of prior studies.&quot;</td>
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### Commonly Used Compound Preparation & Storage Methodologies

- Compounds formulated for injection must be prepared in a sterile manner
  - Use sterile constituents (e.g. sterile powder, sterile diluents)
  - Mix solutions using sterile technique
  - Pass solutions through syringe filter (0.22 µm or finer) at the time of preparation or passage to storage container
- Consideration should be given to diluent used in regard to:
  - Interaction with other constituents
  - Physiologic effect on animal
- Compounds must be stored in a manner to assure maintained sterility
  - Store in sterile container capable of maintaining sterility (e.g. rubber-capped glass blood collection/injection tubes are commonly used for small volumes)
  - Prepare only as much solution as can be used in a reasonable amount of time
  - Maintain proper storage conditions for constituents of solutions (e.g. proper temperature and light-levels)
- Examine preparations before each use
  - Discard if solution is cloudy, precipitated, discolored or otherwise altered
  - Discard or re-filter sterilize if sterility has been compromised
- Assure that pH of solution given by injection is close to physiologic pH
- Pyrogens (including endotoxin contaminants within the laboratory) may cause fever in an animal upon injection regardless of sterility of preparation. While pyrogen testing is not practical for a small amount of preparation the research should consider pyrogenicity as a potential experimental variable when using non-pharmaceutical grade drugs.
- Contact CARE at care@cornell.edu for assistance with acquiring supplies or choosing appropriate compounds and diluents.

### 10. HISTORY

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<tr>
<th>Date</th>
<th>Event</th>
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<tbody>
<tr>
<td>06 JUL 17</td>
<td>Most Recent Annual Review – Reviewed by: B. Blank</td>
</tr>
<tr>
<td>21 SEP 15</td>
<td>New Format – Converted by: J. Kirby</td>
</tr>
<tr>
<td>02 JUN 13</td>
<td>New Issued – Original Author: Dr. B. Blank; Referee: Dr. T. Pavek</td>
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