University of Hawaii IACUC Policy on Use of Non-Pharmaceutical Grade Substances in Research Animals

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IACUC Approval: 1/17/19, 8/18/24

1. Introduction

The Institutional Animal Care and Use Committee (IACUC) maintains oversight review for federally mandated rules and regulations with regard to animal research, ethics, misconduct and biomedical research for the University of Hawaii (UH) System.

2. Policy Statement

This policy is intended to provide information on the requirements of the use of non-pharmaceutical-grade substances in laboratory animals.

Based upon the Regulations and subsequent supplements, the use of non-pharmaceutical grade chemical substances in experimental animals under certain circumstances has been, and will continue to be, a necessary and acceptable component of biomedical research. Use of such compounds at the UH will be based upon:

- scientific necessity;
- non-availability of acceptable veterinary or human pharmaceutical-grade substance(s); and
- specific review and approval by the UH IACUC.

3. Definitions

Pharmaceutical-grade-substance: (from OLAW) 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)).

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.

4. Criteria for the Use of Non-Pharmaceutical-Grade Substances in Laboratory Animals

In their review and deliberation of proposed use of non-pharmaceutical grade substances, issues that the UH IACUC will consider will include:

- safety;
- efficacy;
- the inadvertent introduction of research-complicating variables;
- the goals (clinical vs. research applications);
- the justification provided;
- the level of pain/distress;
- the procedure (survival vs. non-survival);
- quality control (drug preparation, drug properties, drug shelf-life, training/experience/performance of personnel involved;
- known impact on measured experimental outcomes, which is substantiated by data or published reports;
- requirements to produce data that is comparable to previous years' data; and requirements to replicate methods from previous studies.

Cost savings alone cannot adequately justify the use of non-pharmaceutical-grade compounds in animals.

Although the potential animal welfare consequences of complications are less evident in non-survival studies, the scientific issues remain the same, and the principles and need for professional judgment outlined above still apply.

Contingent upon review and approval by the IACUC, non-pharmaceutical grade substances:

- MUST be prepared with sterile diluents.
- MUST be prepared and maintained under sterile conditions.
- MUST be evaluated to assure physiological compatibility
    - pH of solutions should be between 4.5 and 8.0; use outside this range must be justified in the animal use protocol

    - sterility and filtering cannot ensure that pyrogens are not present. Since pyrogen testing is not practical for small lots of prepared solutions, pyrogenicity is a potential experimental variable that researchers must be aware of when using non-pharmaceutical grade agents.
- MUST be clearly labeled with substance names, concentrations, and date of preparation. Since shelf-life of such substances is unknown, long-term storage (> 30 days) is strongly discouraged. Regardless of age, solutions should be discarded if changes in color and/or precipitation occur.
- Should have documentation regarding safety and efficacy consistent with methods of successful use and efficacy in published scientific literature, if available.
- Unused reagents or compounds MUST be discarded in accordance with standard Environmental Health & Safety Office (EHSO) practices.

The UH IACUC realizes that many test compounds and experimental agents are used in research and generally classifies these agents as non-pharmaceutical grade substances without an acceptable pharmaceutical grade alternative. However, PIs should use all available knowledge of the substances to ensure that the aforementioned preparation, evaluation, storage, use, and disposal standards are maintained.

5. <u>Regulations</u>

OLAW: May investigators use non-pharmaceutical-grade compounds in animals?
"OLAW and USDA agree that pharmaceutical-grade substances, when available, must be used to avoid toxicity or side effects that may threaten the health and welfare of vertebrate animals and / or interfere with the interpretation of research results. However, it is frequently necessary to use non-pharmaceutical -grade substances such as investigational compounds, veterinarian or pharmacy-compounded substances, and/or Schedule I controlled substances to meet scientific and research goals.

The IACUC is responsible for evaluating the potential adverse consequences of non-pharmaceutical-grade substances 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.

The IACUC may use a variety of administrative methods to review and approve the use of non-pharmaceutical-grade substances. For example, the IACUC may establish acceptable scientific criteria for use of these substances within the institution, rather than on a case-by-case basis. Investigators and IACUCs should consider relevant animal welfare and scientific issues including safety, efficacy, availability of pharmaceutical-grade substances, and the inadvertent introduction of new variables. **Cost savings alone are not an adequate justification for the use of non-pharmaceutical-grade substances 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.

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 animals must be relieved by sedation, analgesia, or anesthesia using veterinary or human pharmaceutical-grade substances, unless the use of a non-pharmaceutical-grade substance is scientifically necessary, appropriately justified, and approved by the IACUC. The use of a non-pharmaceutical-grade euthanasia agent must meet the same criteria."

Guide for the Care and Use of Laboratory Animals; Eighth edition:
"The use of pharmaceutical-grade chemicals and other substances ensures that toxic and unwanted side effects are not introduced into studies conducted with experimental animals. They should therefore be used, when available, for all animal-related procedures. 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; for example, the use of non-pharmaceutical-grade chemicals of substance may be necessary to meet the scientific goals of a project when a veterinary or human pharmaceutical-grade produce is unavailable. In such instances, consideration should be given to the grade, purity, sterility, pH, pyrogenicity, osmolality, stability, site and route of administration, formulation, compatibility, and pharmacokinetics of the chemical or substance to be administered, as well as animal welfare and scientific issues relating to its use."

AAALAC
"AAALAC distinguishes between two scenarios when considering the use of non-pharmaceutical-grade

compounds:
Clinical Use – compounds used for the clinical treatment of animals and to prevent or reduce/eliminate animal pain or distress. Whenever possible, pharmaceutical grade compounds must be used.
Research Use – compounds used to accomplish scientific aims of the study. If available, and suitable, pharmaceutical grade compounds are preferred."

6. **Tribromoethanol (TBE) Use**:
    a. **Background on Tribromoethanol (formerly available as Avertin®)**
    Tribromoethanol is an injectable anesthetic agent commonly used in mice, and sometimes rats. It was once manufactured specifically for use as an anesthetic by Winthrop Laboratories under the trade name Avertin®, but this product is no longer commercially available. Investigators who wish to use TBE as an anesthetic must therefore make their own solutions. Since TBE is no longer available as a pharmaceutical-grade substance, it is subject to the IACUC policy on the use of non-pharmaceutical grade substance.
    b. **Uses**
    TBE may be an appropriate anesthetic for short term procedures in mice and rats (8-20 minutes), in situations where it will be delivered in single-use and in terminal procedures.
    c. **Common Pharmaceutical Grade Alternatives**
        - Isoflurane
        - Ketamine/xylazine or ketamine/medetomidine
        - Pentobarbital

References:

1. *OLAW Frequently Asked Questions: May investigators use non-pharmaceutical-grade substances in animals?*
2. *https://olaw.nih.gov/faqs#/guidance/faqsGuide for the Care and Use of Laboratory Animals, 8th Edition p. 31*
3. *AAALAC FAQ #9 Non-Pharmaceutical-Grade Compounds*
4. *https://www.aaalac.org/accreditation-program/faqs/#B9*
5. *FDA Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)* *https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book*
6. *FDA Approved Animal Drug Products (Green Book)* *https://www.fda.gov/animal-veterinary/products/approved-animal-drug-products-green-book*