

University of Hawaii IACUC Policy on Use of Non-Pharmaceutical Grade Drugs/Agents in Research Animals

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UH IACUC Approval 1/17/19

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.

Regulations

USDA: Policy 3 states the following regarding use of non-pharmaceutical grade compounds in animal experimentation: Investigators are expected to use pharmaceutical-grade medications whenever they are available, even in acute procedures. Non-Pharmaceutical-grade chemical compounds should only be used in regulated 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 regulated animals.

OLAW: May investigators use non-pharmaceutical-grade compounds in animals?

OLAW and USDA agree that pharmaceutical-grade chemicals and other 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 investigational compounds, veterinarian or pharmacy-compounded drugs, and/or Schedule I controlled substances to meet scientific and research goals.

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.

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."

Policy Statement

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

- Based upon the Regulations and subsequent supplements, the use of non-pharmaceutical grade chemical compounds 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 compound(s); and
 - specific review and approval by the UH IACUC.

Criteria for the Use of Non-Pharmaceutical-Grade Chemicals/Compounds in Laboratory Animals

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

- safety;
- efficacy; and
- the inadvertent introduction of research-complicating variables.
- 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 agents:

- MUST be prepared with sterile diluents
- MUST be prepared and maintained under sterile conditions.
- MUST be evaluated to assure physiological compatibility (e.g., pH, pyrogenicity, osmolarity, etc.)

- MUST be clearly labeled with compound names, concentrations, and date of preparation. Since shelf-life of such compounds 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 be documented 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 compounds without an acceptable pharmaceutical grade alternative. However, PI's should use all available knowledge of the compounds to ensure that the aforementioned preparation, evaluation, storage, use, and disposal standards are maintained.

Tribromoethanol (TBE) Use:

The use of non-pharmaceutical grade chemical compounds, such as Tribromoethanol (TBE), 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 UH will be based upon:

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

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 compound, it is subject to the IACUC policy on the use of non-pharmaceutical grade compounds.

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.

Common Pharmaceutical Grade Alternatives

Isoflurane

ketamine/xylazine or ketamine/medetomidine

pentobarbital

Reference:

- *OLAW Frequently Asked Questions: May investigators use non-pharmaceutical-grade substances in animals?*
 - <https://olaw.nih.gov/guidance/faqs>
- *Guide for the Care and Use of Laboratory Animals, Eighth Edition Page 31*
- *USDA Policy #3*
 - http://www.aphis.usda.gov/animal_welfare/policy.php?policy=3
- *AAALAC FAQ #9 Non-Pharmaceutical-Grade Compounds*
 - http://www.aaalac.org/accreditation/faq_landing.cfm#B9