



# Use of Non-Pharmaceutical Grade Drugs in Research and Extension Animals

Peter Autenried, Campus Veterinarian

Version November 18, 2015

## **Preamble**

*A pharmaceutical grade drug is a 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). OLAW and USDA state that pharmaceutical-grade chemicals and other substances, when available, must be used to avoid side effects that may threaten the health and welfare of vertebrate animals or interfere with the interpretation of research results.*



## Contents

I. Definitions.....	2
II. Scope.....	3
III. Policy.....	3
A. Mandate To Use Pharmaceutical Grade Drugs.....	3
B. IACUC Criteria Applied For Approval of Non-Pharmaceutical Grade Drugs, Agents, And Compounds.....	3
IV. Procedures.....	4
C. Selection of Compounds for use in Research.....	4
D. Expired Agents.....	4
E. Consideration of Non-Pharmaceutical Grade Compounds For Use In Research.....	4
F. Specific Compounds Subject to Institution-Wide Policy.....	5
1. Pentobarbital Sodium.....	5
2. Tribromoethanol (Avertin®).....	5
3. Tricainemethanesulfonate (TMS, MS-222®, Tricaine®-S).....	6
4. Urethane, $\alpha$ -Chloralose, and Chloral Hydrate.....	6
5. New Investigational Compounds.....	6
V. References.....	6

### I. Definitions

- a. **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.
- b. **Analytical Grade Bulk Chemical:** ~99% purity; certificate of analysis is usually available
- c. **Non-availability:** Not commercially available from an active US vendor; includes formulations supplied as tablet, capsule, injectable, etc.
- d. **Investigational New Drug (IND) Program:** The FDA's Investigational New Drug (IND) program is the means by which a pharmaceutical company obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved. The FDA reviews the IND application for safety to assure that research subjects will not be subjected to unreasonable risk. If the application is cleared, the candidate drug usually enters a Phase 1 clinical trial. Regulations are primarily at 21 C.F.R. § 312.
- e. **Investigational New Animal Drug (INAD):** A set of guidelines provided by the FDA how to investigate and document a new or existing drug for licensing for a specific indication in a new species



- f. **FDA:** Food and Drug Administration; FDA approved compounds are manufactured using USP/NF compounds
  - i. **Primary Standards:** These are produced according to the national pharmacopeias, such as USP and BP.
  - ii. **Secondary Standards:** These are produced by other entities such as Sigma, a compounding pharmacy, or a pharmaceutical company. They test the quality and purity of secondary standards and compare these to primary standards.
- g. **Expired agent:** A pharmaceutical-grade agent that has exceeded its printed expiration date as indicated on the label printed by the manufacturer
- h. **Survival (Non-Terminal) Procedure:** A procedure performed on an anesthetized or an awake animal from which the animal will recover
- i. **Non-Survival (Terminal) Procedure:** A procedure that requires anesthesia performed on an animal in which the animal is euthanized prior to anesthetic recovery

## II. Scope

This policy applies to all drugs, agents, and compounds to be administered to all animals used at the University of Idaho, including analgesics, anesthetics, investigational drugs, and fluids used for any purpose.

## III. Policy

This policy ensures regulatory compliance with USDA and PHS guidelines regarding the mandate to use pharmaceutical grade drugs in research and extension animals when such drugs are available and the criteria that must be met for IACUC approval of non-pharmaceutical grade compounds used in research and extension animals held at UI.

### A. Mandate to Use Pharmaceutical Grade Drugs

Investigators must use pharmaceutical-grade compounds whenever they are available, even for non-survival procedures.

### B. IACUC Criteria Applied For Approval of Non-Pharmaceutical Grade Drugs, Agents, and Compounds

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.

The following criteria apply:

- a. A scientific justification is required to use non-pharmaceutical-grade compounds in experimental animals if a pharmaceutical grade drug or alternate pharmaceutical grade drug is available for the same outcome.
- b. Cost savings alone is not a justification for using non-pharmaceutical grade compounds in research or extension animals.
- c. Expired anesthetics, analgesics, or sedatives may never be used. The use of other expired agents and materials is limited to non-survival (terminal) procedures. Non-expired agents must be used for all survival (non-terminal) procedures unless specifically approved by the IACUC.



#### IV. Procedures

##### C. Selection of Compounds for use in Research

When selecting compounds for use in research the following order of choice should be applied:

- a. FDA approved veterinary or human pharmaceutical compounds;
  - i. **The Orange Book**, the database maintained by FDA listing approved commercial formulations for human drugs
  - ii. **The Green Book**, the database maintained by FDA listing approved commercial formulations for veterinary drugs
- b. 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 or volume for a given species.
- c. 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.
- d. Analytical grade bulk chemical used to compound a needed dosage form (requires justification);
- e. Other grades and sources of compounds (requires justification).

##### D. Expired Agents

- a. PI's are responsible to regularly check their pharmaceutical agents both in their laboratories and in the facilities where they keep their animals to ensure they are not using drugs on animals that are expired.
- b. Facility managers are responsible to regularly check shared pharmaceutical agents used anywhere within their animal facilities they are managing.
- c. When drugs are compounded, the expiration date of such aliquots cannot be past the expiration date of any of its components including diluents.
- d. Expired agents must be clearly labeled "not for animal use" and must be stored separately from non-expired drugs used in animals.
- e. Expired controlled drugs must be disposed of via the Campus Veterinarian. All other compounds must be disposed of via Environmental Health and Safety (EHS).

##### E. Consideration of Non-Pharmaceutical Grade Compounds For Use in Research

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.

The IACUC may approve the use of non-pharmaceutical-grade substances in the following situations:

- a. If no equivalent veterinary or human drug is available for experimental use, then the highest- grade equivalent chemical reagent should be used and formulated aseptically and with a non-toxic vehicle as appropriate for the route of administration.



- b. Although an equivalent veterinary or human drug is available for experimental use, the chemical-grade reagent is required to replicate methods from previous studies because results are directly compared to those of replicated studies.
- c. Although an equivalent veterinary or human drug is available, dilution or change in formulation is required.
  - i. If adulteration by dilution, addition, or other change in formulation is required, there may be no additional advantage to be gained by using the USP formulation.
  - ii. 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.
  - iii. PIs use professional judgment to determine the appropriate test material and to ensure use of an agent with the least likelihood for causing adverse effects.
- d. The available human or veterinary drug is not concentrated enough to meet experimental requirements.
- e. The available human or veterinary drug does not meet the non-toxic vehicle requirements for the specified route of administration.
- f. The pharmaceutical grade drug is not currently commercially available in the US.

## **F. Specific Compounds Subject to Institution-Wide Policy**

### **1. Pentobarbital Sodium**

- a. 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.
- b. For many species, adulteration by dilution, addition, or other change in formulation is required. Therefore, there may be no additional advantage to be gained by using the USP formulation.

### **2. Tribromoethanol (Avertin®)**

Avertin® is the trade name for the injectable anesthetic tribromoethanol. Avertin® was once manufactured as a pharmaceutical-grade drug, but it is no longer available. There are multiple reports in the literature of physiologic harm to animals including ileus, adhesions, and mortality from the use of tribromoethanol. OLAW has advised IACUCs to critically evaluate the proposed use of tribromoethanol and the consideration of alternative methods that avoid or minimize discomfort, distress and pain. OLAW has learned of journals turning down studies for publication that described use of tribromoethanol.

The preparation and use of tribromoethanol must be scientifically necessary, appropriately justified and approved by the IACUC:

- a. Other injectable anesthetics, such as ketamine, xylazine, midazolam, and etomidate, which are available as FDA approved veterinary or human pharmaceutical compounds, can provide similar planes of anesthesia and duration of action, and have fewer reported adverse effects than tribromoethanol.



- b. Justification for using tribromoethanol should take into account the availability of commercially available pharmaceutical-grade alternatives and include a rationale for why these alternatives cannot be used.
- c. Tribromoethanol is not controlled by the Drug Enforcement Administration (DEA); justification solely based on this fact, however, is not considered scientific or adequate.
- d. Cost or convenience is not a scientific or adequate justification for the use of tribromoethanol.
- e. If tribromoethanol will be used for anesthesia, it must be properly prepared and stored.

### **3. Tricainemethanesulfonate (TMS, MS-222®, Tricaine®-S)**

Tricainemethanesulfonate is the anesthetic of choice for immersion anesthesia for most fish and amphibian species. It is available as a pharmaceutical-grade compound from Western Chemical Inc. under the trade name Tricaine®-S. Investigators are expected to use this product, unless scientific justification is provided for why a non-pharmaceutical grade product such as Sigma's is used. Please note: Tricainemethanesulfonate must be pH adjusted before use.

### **4. Urethane, $\alpha$ -Chloralose, and Chloral Hydrate**

Urethane,  $\alpha$ -chloralose, and chloral hydrate have been used as injectable anesthetic agents in laboratory animals, particularly rodents. They are not available as pharmaceutical-grade compounds. Although pharmaceutical-grade alternative anesthetics are available, urethane,  $\alpha$ -chloralose, and chloral hydrate still have important roles as anesthetic agents in biomedical research due to unique physiologic effects (for example, urethane has minimal respiratory effects).

The preparation and use of urethane,  $\alpha$ -chloralose, or chloral hydrate must be scientifically necessary, appropriately justified and approved by the IACUC:

- a. Scientific justification should be provided for the use of urethane,  $\alpha$ -chloralose, or chloral hydrate instead of commercially available, pharmaceutical-grade injectable anesthetics.
- b. Use of urethane,  $\alpha$ -chloralose, and chloral hydrate should be limited to terminal procedures.
- c. Urethane is considered a carcinogen and mutagen. Preparation, use, and disposition of this compound should take into account these hazards, and appropriate safety precautions should be reflected in the IACUC protocol, approved by Radiation Safety (located within EHS), and implemented by laboratory personnel.

### **5. New Investigational Compounds**

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.

## **V. References**

- a. The Guide for the Care and Use of Laboratory Animals, 8th Edition



- b. Animal Welfare Act
- c. U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care, Policy 3- Veterinary Care, April 14, 1997.
- d. Frequently asked questions about the public health service policy on humane care and use of laboratory animals. Wolff A, Garnett N, Potkay S, Wigglesworth C, Doyle D, Thornton V. Lab Animal (NY). 2003 Oct;32(9):33-6.
- e. United States Pharmacopeia Website - <http://www.usp.org/usp-nf>
- f. OLAW Webinar, "Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals," June 4, 2015