Background

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 and/or interfere with the interpretation of research results.

SCOPE

This policy applies to all agents and compounds administered to laboratory animals for research, teaching and testing, including analgesics, anesthetics, investigational drugs, and fluids used for these purposes.

POLICY

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

II. The use of non-pharmaceutical-grade compounds in experimental animals requires IACUC approval and may be an acceptable practice under certain circumstances, based on:
   A. Scientific necessity;
   B. Non-availability of an acceptable veterinary or human pharmaceutical-grade compound;
   C. Non-availability of an acceptable alternative pharmaceutical-grade compound

III. Cost savings alone is not a justification for using non-pharmaceutical grade compounds in laboratory animals.

IV. The use of investigational compounds to meet research goals may be used with IACUC approval.

V. 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.

VI. Expired anesthetics, analgesics or sedatives may never be used. The use of other expired agents 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.

PROCEDURES

SELECTION OF COMPOUNDS FOR USE IN RESEARCH

I. When selecting compounds for use in research the following order of choice should be applied:
   A. FDA approved veterinary or human pharmaceutical compounds;
   B. The Orange Book, the database maintained by FDA listing approved commercial formulations for human drugs
**C. The Green Book**, the database maintained by FDA listing approved commercial formulations for veterinary drugs

**II. 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.**

**III. 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.**

**IV. Analytical grade bulk chemical used to compound a needed dosage form (requires justification);**

**V. Other grades and sources of compounds (requires justification).**

**EXPIRED AGENTS**

**I. Stocks of pharmaceutical agents should be checked regularly to ensure they have not passed their expiration dates.**

**II. Expired agents must be clearly labeled to indicate that they are expired.**

**III. Expired agents should be stored separately from non-expired agents.**

**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

**EXAMPLES FOR USE OF NON-PHARMACEUTICAL-GRADE SUBSTANCES** - The IACUC may approve the use of non-pharmaceutical-grade substances in the following situations:

**I. 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.**

**II. 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.**

**III. Although an equivalent veterinary or human drug is available, dilution or change in formulation is required.**

   **A. 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.**

   **B. 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.**

   **C. Professional judgment should be used to determine the appropriate test material and to ensure use of an agent with the least likelihood for causing adverse effects.**

**IV. The available human or veterinary drug is not concentrated enough to meet experimental requirements.**

**V. The available human or veterinary drug does not meet the non-toxic vehicle requirements for the specified route of administration.**

**VI. The pharmaceutical grade drug is effectively unavailable.**

**SPECIFIC COMPOUNDS SUBJECT TO INSTITUTION-WIDE POLICY**

**I. 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.

II. 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. 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.

A. 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.

B. If tribromoethanol will be used for anesthesia, it must be properly prepared and stored.

III. 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 available as a pharmaceutical-grade compound under the trade names Finquel® or Tricaine®-S. Investigators are expected to use one of these two products, unless scientific justification is provided for why neither product may be used.

IV. Urethane, α-chloralose, and chloral hydrate

A. Urethane, α-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, α-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).

B. Scientific justification should be provided for the use of urethane, α-chloralose, or chloral hydrate instead of commercially available, pharmaceutical grade injectable anesthetics.

C. Use of urethane, α-chloralose, and chloral hydrate should be limited to terminal procedures.

D. 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 Environmental Health & Radiation Safety, and implemented by laboratory personnel.

V. New investigational compounds

A. 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.

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.

Analytical grade bulk chemical: ~99% purity; Certificate of Analysis is usually available

Non-availability: Not commercially available from an active US vendor; includes formulations supplied as tablet, capsule, injectable, etc.

New investigational compound: Supplied by its manufacturer for testing in an experimental setting only and for this reason would not have chemical purity standards established; by default is considered a non-pharmaceutical grade compound for which there is no acceptable hum

FDA: Food and Drug Administration; FDA approved compounds are manufactured using USP/NF compounds

Primary standards: are produced according to the national pharmacopeias, such as USP and BP.

Secondary standards: 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.

Expired agent: a pharmaceutical-grade agent that has exceeded its printed expiration date as indicated on the label printed by the manufacturer.

Survival (non-terminal) procedure: A procedure performed on an anesthetized or an awake animal from which the animal will recover.

Non-Survival (terminal) procedure: procedure that requires anesthesia performed on an animal in which the animal is euthanized prior to anesthetic recovery.

AUTHORITY

Animal Welfare Act

REFERENCES
U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care, Policy 3-Veterinary Care, April 14, 1997.


OLAW Webinar, “Use of Non-Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals”, March 1, 2012