THE USE OF NON-PHARMACEUTICAL GRADE COMPOUNDS

The University of Pennsylvania Institutional Animal Care and Use Committee (IACUC) has developed the following policy to help research investigators properly reconstitute, store, and use non-pharmaceutical drugs. It is the responsibility of the Principle Investigator (PI) to institute adequate inventory and laboratory management procedures to ensure that any drug is properly prepared, identified, and stored. Deviations from or modifications to the policy must be requested of, and approved by, the IACUC. This policy applies to all Penn research related-animal activities that fall under the IACUC’s jurisdiction.

The use of non-pharmaceutical substances with undefined or higher levels of impurities or poorly formulated non-commercial preparations can introduce unwanted experimental variables or even toxic effects; however their need cannot always be avoided. In compliance with the NIH and USDA regulations, non-pharmaceutical grade drugs are to be used in live animals only when there is no pharmaceutical grade alternative available unless there is a scientific justification approved by the IACUC.

USDA Policy #3 states, “Pharmaceutical grade compounds are to be used whenever available. The IACUC should develop a consistent evaluation process which includes but is not limited to the scientific justification and the availability of an acceptable veterinary or human pharmaceutical-grade product. Cost savings alone is not sufficient justification for using a non-pharmaceutical –grade substance...”. OLAW agrees with the USDA’s position (OLAW FAQ F4).

This policy offers direction on the following topics:
- Definitions
- Justifications for the use of non-pharmaceutical compounds
- Reconstitution of non-pharmaceutical grade compounds for parenteral use
- Common pharmaceutical grade excipients and vendors

DEFINITIONS

**USP/NF (United States Pharmacopeia/National Formulary):** USP/NF is an official public standards-setting authority for all prescription and over-the-counter medicines and other health care products manufactured and sold in the United States. The letters “USP” are typically listed on a label after the drug name (e.g., sodium bicarbonate injection USP).

**Pharmaceutical grade compound:** Pharmaceutical grade refers to a USP-established standard or level of purity suitable for the production of drugs/biologics/reagents, and approved by the Food and Drug Administration (FDA). The FDA maintains a database listing of FDA-approved commercial formulations for both FDA-approved human drugs (Orange Book), veterinary drugs (Green Book), and legally marketed unapproved new animal drugs. Any difficulties in finding...
IACUC Policy
THE USE OF NON-PHARMACEUTICAL GRADE COMPOUNDS

compounds on any of the fore-mentioned links may be due to misspellings. Compounds spelled incorrectly could lead to false negative searches.

For a majority of common substances, including excipients, used in laboratory animal research, pharmaceutical grade (USP or NF grade) substances are available and should be used. Examples of common substances that are available in USP or NF grades include:
- 0.9% Saline
- DMSO (dimethyl sulfoxide)
- Corn oil/mineral oil
- Tamoxifen
- Tetracycline/Doxycycline
- Analgesics (e.g., meloxicam, buprenorphine)
- Anesthetics (e.g., ketamine, isoflurane)
- Medical or industrial grade compressed gases (CO₂, O₂)
- Neuromuscular blockers (e.g., pancuronium)
- Euthanasia reagents (e.g., potassium chloride, Euthasol)

**Non-pharmaceutical grade compound:** This refers to an analytical grade bulk chemical agent that has not been formulated for the production of medicine. Compounds distributed by “chemical vendors” (e.g., Fisher Scientific, Sigma-Aldrich) are not pharmaceutical grade. Common examples of non-pharmaceutical grade agents requiring special formulation are tamoxifen and pentobarbital.

**New investigational compound:** These are supplied by a manufacturer for testing in an experimental setting only and for this reason would not have chemical purity standards established. By default new investigational compounds are considered non-pharmaceutical grade.

**Parenteral use:** This denotes any route other than the alimentary canal, such as intravenous (IV), subcutaneous (SC), intramuscular (IM), retro-orbital (RO), intraperitoneal (IP), or intracranial (IC).

**Enteral use:** This specifically refers to administration via the alimentary canal, such as oral gavage, *per os* (PO), or as an additive to water/food.

**Excipient:** An inert substance that acts as a vehicle for a drug or compound.

**JUSTIFICATIONS FOR THE USE OF NON-PHARMACEUTICAL GRADE COMPOUNDS**

The NIH Office of Laboratory Animal Welfare (OLAW) states it would be reasonable for the IACUC to review and approve the use of non-pharmaceutical grade substances in the situations itemized below. These specific scenarios should then be captured within the protocol, as applicable.
IACUC Policy
THE USE OF NON-PHARMACEUTICAL GRADE COMPOUNDS

1) No equivalent veterinary or human drug is available for experimental use; therefore, the highest-grade equivalent chemical reagent will be used and formulated aseptically and with a non-toxic vehicle as appropriate for the route of administration.
   a. Based on OLAW guidance, one exception is non-pharmaceutical grade pentobarbital. 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 urethane and tribromoethanol use in mice and rats, a scientific justification and a description of why pharmaceutical grade alternatives (e.g. ketamine/xylazine, isoflurane, etc.) cannot be used in a given animal model will be considered by the IACUC.

2) An equivalent veterinary or human drug is available for experimental use; however the chemical-grade reagent is required to replicate methods from previous studies because results are directly compared to those of replicated studies.

3) The available human or veterinary drug is not concentrated enough to meet experimental requirements or the correct formulation for the route of administration.

4) The available human or veterinary drug contains preservatives or inactive ingredients which confound the research goals of the study.

In developing and reviewing protocols, the investigator and IACUC should consider animal welfare and scientific issues related to the use of non-pharmaceutical grade substances, including the potential for contamination, safety, efficacy, and the inadvertent introduction of confounding research variables. For all non-pharmaceutical grade substances listed in the ARIES protocol, a justification should be given by either selecting from the list of conditions provided on the Drug tab (which is consistent with this policy) or by describing other circumstances.

For all non-pharmaceutical grade substances used in animals, the PI will use the highest grade/purity available that meets the requirements of the study and formulate the final product to maintain sterility, stability, physiological compatibility (e.g., pH, osmolality, and pharmacokinetics appropriate for the site/route of administration), and quality control, and to minimize pyrogenicity.

RECONSTITUTION OF NON-PHARMACEUTICAL GRADE COMPOUNDS FOR PARENTERAL USE

1) Must be prepared to USP/NF standards for sterility; at a minimum, preparation of non-pharmaceutical drug should be within a clean laminar flow hood, while minimizing contamination of the product.

2) Must have a label with the following information, at minimum:
   a. Compound name
   b. Compound concentration
IACUC Policy
THE USE OF NON-PHARMACEUTICAL GRADE COMPOUNDS

c. Date of reconstitution

3) Solutions derived from non-sterile components must be filtered (0.22 µm or finer) into sterile, sealed containers. A very viscous product may require a filter with a larger pore size, but this increases the chance of improper sterilization and may require verification of sterility.

4) Date of expiration: The preparation of compounds from bulk, non-sterile components is always at high risk for microbial contamination. Therefore, unless indisputable efficacy and quality assurance data can be provided that substantiates a more generous expiration date, the following must apply:

a. All agents must be stored based upon agent-specific stability and compatibility (i.e., propofol will be discarded within 8 hours of opening, diazepam is adsorbed by plastic and as such cannot be stored in syringes or IV bags/lines, Avertin has specific storage requirements) and manufacturer-recommended temperatures, duration, and protection from light as applicable.

b. All reconstituted agents will be discarded based upon the component with the shortest expiration date, manufacturer recommendations, or within 30 days, whichever occurs first. No reconstituted agents or combination agents may be maintained for longer than 30 days.

c. Upon use, sterile supplies (e.g., syringes) must be used for administration of the agent.

d. Agents may be stored in a sterile syringe, bottle, or tube if they will be used the same day they are reconstituted. Otherwise, if the agent will be maintained for use after the day of reconstitution, a sterile vial or tube with a rubberseal that does not need to be removed for withdrawal of the agent (i.e., the seal can be punctured with a syringe) must be used to maintain sterility.

COMMON PHARMACEUTICAL GRADE EXCIPIENTS AND VENDORS

1) 0.9% Saline – multiple sources (e.g., VHUP and HUP Pharmacies, Baxter Healthcare Corp.)

2) Ethanol – multiple sources

3) Mineral oil – USP grade commonly found in most drug stores (e.g., Walgreens, CVS)

4) Corn oil – USP grade can be found at:

5) DMSO – USP grade can be found at:
IACUC Policy
THE USE OF NON-PHARMACEUTICAL GRADE COMPOUNDS

REFERENCES

2) U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care, Policy 3-Veterinary Care, March 7, 2014.
7) http://pharmlabs.unc.edu/labs/parenterals/filters.htm

OTHER USEFUL RESOURCES

2) For more information about FDA-approved veterinary products: Animal Drugs @ FDA
3) For more information on FDA-approved human products: Drugs@FDA: FDA Approved Drug Products
4) For more information FDA and pharmacy compounding: http://www.youtube.com/watch?feature=player_detailpage&v=kif_rmtIQb0