IACUC Guidelines on the use of Non-pharmaceutical Grade Compounds in Animal Use Protocols

The use of non-pharmaceutical grade compounds in research animals REQUIRES IACUC approval.

The University of Maryland Baltimore (UMB) Institutional Animal Care and Use Committee (IACUC) has developed the following guidelines to help investigators properly reconstitute, store, and use non-pharmaceutical drugs. It is the responsibility of the Principal 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 these guidelines must be requested of, and approved by, the IACUC. This policy applies to all research related-animal activities that fall under the UMB 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[1], 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. Cost savings alone are not an adequate justification for the use of non-pharmaceutical-grade substances in animals.

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 diluents or vehicles 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[3]. The letters "USP" are typically listed on a label after the drug name (e.g., sodium bicarbonate injection USP).

Pharmaceutical grade drug/ compounds: Pharmaceutical grade refers to a USP-established standard or level of purity, with defined bioavailability, routes and half-life of elimination of the specific drug /compound produced under GMP (Good Manufacturing Practices), 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 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 diluents or vehicles, 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)
- Mineral oil
- Tamoxifen
- Tetracycline/Doxycycline
- Analgesics (e.g., meloxicam, buprenorphine)
- Anesthetics (e.g., ketamine, Isoflurane)
- Medical or industrial grade compressed gases (CO2, O2)[7,8]
- 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 USP grade product. *Compounds distributed by "chemical vendors" (e.g., Fisher Scientific, Sigma-Aldrich) are not pharmaceutical grade*. A common example of a non-pharmaceutical grade agent requiring special formulation is pentobarbital (see UMB IACUC Policy on the Use of Non-Pharmaceutical Grade Sodium Pentobarbital).

New investigational drug/ 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 or administration per rectum.

JUSTIFICATIONS FOR THE USE OF NON-PHARMACEUTICAL GRADE COMPOUNDS

The NIH Office of Laboratory Animal Welfare (OLAW)[2,4] 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.

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 (see UMB IACUC Policy on the Use of Non-Pharmaceutical Grade Sodium Pentobarbital).
    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 PI 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. Justification must be provided for all non-pharmaceutical grade substances listed in the protocol.

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 in a sterile manner.
2) 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.
3) The final product must have a label with the following information, at minimum:
    a. Compound name, final concentration (mg/ml) and total volume (ml) in vial for injection.
    b. Preparation date and initials of preparer.
    c. Date of expiration (*as below*)
4) Date of expiration: The preparation of compounds from bulk, non-sterile components is always at high risk for microbial contamination[6]. Therefore, unless indisputable efficacy and quality assurance data can be provided that substantiates a more generous expiration date, the following must apply:
    a. All reconstituted agents will be discarded based upon the component with the shortest expiration date, manufacturer recommendations, or within 30 days, whichever occurs first.
    b. No reconstituted agents or combination agents may be maintained for longer than 30 days unless specifically indicated on the USP label.
    c. All agents must be stored based upon agent-specific stability, compatibility and manufacturer-recommended temperatures, duration, and protection from light, as applicable.
    d. Agents must be stored in appropriate drug bottles / vials, please review the Drug Dilution & Storage Guidelines. If the agent will be maintained for use after the day of reconstitution, it must be handled aseptically to maintain sterility.
    e. Sterile supplies (*e.g., syringes*) must be used for administration of the agent.

NOTE:

- Use of reconstituted agents beyond 30 days requires scientific justification based on published, peer-reviewed literature and/or evidence proving that the agent remains stable, efficacious, and sterile for the proposed storage time. An exemption to use reconstituted agents beyond 30 days must be detailed in the protocol and approved by the IACUC.
- Evaluate reconstituted agents prior to administration for signs of contamination (e.g., discoloration, cloudiness, floaters, etc.). Agents must be discarded and replaced (as needed) if signs of contamination are observed.

COMMON PHARMACEUTICAL GRADE DILUENTS OR VEHICLES AND VENDORS

Diluents or vehicles are required to be pharmaceutical grade for all mammals except mice and rats.

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:
    a. http://whc-oils.com/usp-nf-oil-supplier.html (also includes other USP-grade oils)
    b. http://www.parchem.com/chemical-supplier-distributor/Corn-Oil-USP-008663.aspx

OTHER USEFUL RESOURCES

1) Education Resources: Office of Laboratory Animal Welfare: Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals – June 4, 2015
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 Drugs

REFERENCES

1) Office of Laboratory Animal Welfare: https://olaw.nih.gov/faqs#/guidance/faqs, Section F: Animal use and Management, Question 4.
2) Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals – June 4, 2015, OLAW online seminar: https://olaw.nih.gov/education/educational-resources/webinar-2015-06-04.htm
3) USP Reference Standards Listing and Catalog: http://www.usp.org/reference-standards/find-reference-standard
4) 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, Thorton, V.Lab Animal (NY). 2003. October; 32(9):33-6.
5) The United States Pharmacopeia, 27th rev., and the National Formulary 22nd ed. USP General Information Chapter. Pharmaceutical Compounding–Sterile Preparations. Rockville, MD: The United States Pharmacopeial Convention, 2003.
6) Guidelines for Euthanasia of Rodents Using Carbon Dioxide, NIH Office of Animal Care and Use: http://oacu.od.nih.gov/ARAC/documents/Rodent_Euthanasia_Adult.pdf
7) AVMA Guidelines for the Euthanasia of Animals: 2020 Edition. https://www.avma.org/KB/Policies/Documents/euthanasia.pdf

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