Subject: Use of Non-Pharmaceutical Grade Drugs

BACKGROUND

OLAW and USDA consider that the use of any non-pharmaceutical grade (non-USP*) compound should be based on: scientific necessity; no availability of an acceptable veterinary or human pharmaceutical-grade compound; and specific review and approval by the IACUC. ¹, ²

DEFINITIONS

1. Pharmaceutical grade compound: Drug, biologic, reagent, etc. which is approved by the FDA or for which a chemical purity standard has been written/established by USP/NF, BP.
2. Analytical grade bulk chemical: ~99% purity; Certificate of Analysis is usually available
3. Non-availability: Not commercially available from an active US vendor; includes formulations supplied as tablet, capsule, injectable, etc.
4. 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
5. USP/NF: United States Pharmacopeia/National Formulary. The United States Pharmacopeia (USP) is an official public standards-setting authority for all prescription and over-the-counter medicines.
6. BP: British Pharmacopeia
7. FDA: Food and Drug Administration; FDA approved compounds are manufactured using USP/NF compounds

PRINCIPLE

The use of pharmaceutical-grade compounds in laboratory animals ensures that the compounds administered meet established documentable standards of purity and composition which in turn help ensure research animal health and welfare, as well as the validity of experimental results. The use of lower grade chemicals/compounds with higher levels of impurities or poorly formulated non-commercial preparations can introduce unwanted experimental variables or even toxic effects, and so should be avoided if at all possible.

Although pharmaceutical grade compounds should be used in experimental animals whenever possible, the use of non-pharmaceutical-grade compounds in experimental animals is an acceptable practice under certain circumstances. For example, in the case of new investigational compounds, they would be the only grade and formulation available.

The NIH Office of Laboratory Animal Welfare (OLAW) and the United States Department of Agriculture (USDA) both have determined that the use of non-pharmaceutical-grade compounds should be based on (1) scientific necessity, (2) non-availability of an acceptable veterinary or human pharmaceutical-grade compound, and (3) specific review and approval by the IACUC. Cost savings alone is not considered an adequate justification for the use of non-pharmaceutical-grade compounds in laboratory animals.

OLAW has also stated that while the possible implications of the use of non-pharmaceutical grade compounds in non-survival studies appears less evident, the scientific issues remain the same and professional judgment, as outlined above, must still apply.

It is important to understand that this guideline pertains to all components, both active and inactive, contained in the preparation to be administered. Therefore, the vehicle used to facilitate administration of a compound is as important of a consideration as the active compound in the preparation.
IACUC Policy

Pharmaceutical Grade Compounds must be used, when available, for all animal-related procedures.

When selecting compounds the following order of choice should be applied:

- FDA approved veterinary or human pharmaceutical compounds;
- FDA approved veterinary or human pharmaceutical compounds used to compound a needed dosage form;
- USP/NF or BP pharmaceutical grade compound used in a needed dosage form;
- Analytical grade bulk chemical used to compound a needed dosage form (requires justification);
- Other grades and sources of compounds (requires justification).

NOTE: For new investigational drugs the grade and formulation is not optional, but the investigator and IACUC can verify health and safety issues described below.

Non-pharmaceutical-grade Compounds can only be used in research activities utilizing animals if reviewed and approved by the IACUC. The following circumstances must be met for consideration by the IACUC:

- The research activity requires the use of non-pharmaceutical-grade compounds for reason of scientific necessity.
- Acceptable veterinary or human pharmaceutical-grade products are not available (most novel compounds are in this category).
- Cost savings alone is not an adequate justification for using non-pharmaceutical-grade compounds in animals.
- For all species, any non-pharmaceutical chemical agents administered parenterally (by injection) must be sterile and maintained in a sterile container. All containers must be legibly labeled to provide the mixing and expiration dates and the name and concentration of the primary compound. This includes both the primary containers (e.g. vial, bottle) and secondary containers (e.g. syringes, fluid bags).
  - Compounds drawn into syringes do not need to be labeled if they will be used immediately.
  - If alternative methods of labeling are required they must be described in the animal care protocol.

Guidelines for Non-pharmaceutical-grade Compound Use:

When developing and reviewing a proposal to use non-pharmaceutical grade compounds, the PI and IACUC should 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.

For all compound use, the IACUC should consider the grade/purity being proposed, the formulation of the final product, and issues such as sterility, pyrogenicity, stability, pH, osmolality, site/route of administration, pharmacokinetics, physiological compatibility, and quality control.

Recommendations for Protocol Applications:

Protocols should include the following information when a non-pharmaceutical grade product is utilized:

- Chemical grade of compound (see definitions above)
- Source
- Formulation and vehicle for compound
- Preparation of compound (if applicable)
- Storage conditions and shelf-life (if applicable)
Pentobarbital

Pentobarbital is a commonly used anesthetic. The recent exorbitant cost increases of the only commercially-prepared pentobarbital solution, Nembutal®, have placed it logistically into the unavailable category. Alternatively, pentobarbital is available through compounding pharmacies at a lower price than Nembutal. The use of compounded pentobarbital for anesthesia is considered acceptable. All other forms of pentobarbital must be approved on a case-by-case basis by the WSU IACUC.

A pentobarbital euthanasia solution (such as Fatal Plus) may not be used as an anesthetic for survival or non-survival procedures. OLAW in concert with USDA agree that a procedure may be performed as a part of euthanasia. And this would be limited to terminal perfusion or exsanguination. In both cases, death is an immediate outcome of the procedure. Therefore, euthanasia solution may be used for terminal perfusion or exsanguination procedures.

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1 PHS Policy on Humane Care and Use of Laboratory Animals, Frequently Asked Questions: May investigators use non-pharmaceutical grade compounds in animals? (updated: 11/19/2012)

2 United States Department of Agriculture, Animal and Plant Inspection Service, Veterinary Medicine, Animal Care: Animal Care Resource Guide, Policy #3

3 Use of Non-Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals. Transcript from Office of Laboratory Animal Welfare Online Seminars. March 1, 2012