Guidelines for Use of Non-Pharmaceutical Grade Drugs

James Madison University
Institutional Animal Care and Use Committee

Purpose: 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.

The use of non-pharmaceutical-grade compounds in laboratory animals should be clearly delineated and justified in the protocol application before it will be approved by the IACUC. James Madison University abides by the OLAW and USDA recommendations and therefore discourages the use of non-pharmaceutical grade drugs.

Definition:

Pharmaceutical Grade -- 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. Pharmaceutical grade drugs are marketed for veterinary or human use.

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
USP/NF: United States Pharmacopeia/National Formulary

BP: British Pharmacopeia

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

Recommendations for use:

When reviewing a protocol to use non-pharmaceutical grade compounds the IACUC must 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. Non-pharmaceutical-grade compounds should be requested only for reasons of scientific necessity or lack of available veterinary or human pharmaceutical-grade products. **Cost savings will not be considered adequate justification for using non-pharmaceutical grade compounds in animals.**

For all compound use, the IACUC will 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.

When selecting compounds the following order of choice should be applied:
1. FDA approved veterinary or human pharmaceutical compounds;
2. FDA approved veterinary or human pharmaceutical compounds used to compound a needed dosage form;
3. USP/NF or BP pharmaceutical grade compound used in a needed dosage form;
4. Analytical grade bulk chemical used to compound a needed dosage form (requires justification);
5. Other grades and sources of compounds (requires justification).

Creating compounds: For all species, any non-pharmaceutical chemical agents administered parenterally (by injection) in survival studies should be sterile, maintained in a sterile container, and labeled to provide the mixing date, name and concentration of the compound as well as its expiration date. Heat-stable compounds may be sterilized by autoclaving, and those that are not heat stable can be sterilized by microfiltration. The investigator is responsible for determining the "shelf" life for the compound after being dissolved in solvent. If the "shelf life" is not obtainable, it is recommended that the solution be prepared each day it is used.

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

References:

1 U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care, Policy 3-Veterinary Care, April 14, 1997. :
2 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.