THE USE OF NON-PHARMACEUTICAL GRADE SUBSTANCES IN THE UA ANIMAL CARE & USE PROGRAM

POLICY: This policy provides a definitive position on the use of non-pharmaceutical grade substances in the UA animal care & use program.

BACKGROUND/PURPOSE: Procedures involving animals, including the use of drugs, medical materials, anesthetics, analgesics and euthanasia agents are regulated by the Office of Laboratory Animal Welfare (OLAW), the U.S. Department of Agriculture (USDA), the Public Health Service Policy on Humane Care and Use of Laboratory Animals, and the Animal Welfare Act(AWA, 9 CFR, §2.33).

The use of pharmaceutical-grade substances in laboratory animals ensures that the substances administered meet established documentable standards of purity and composition. This in turn helps ensure research animal health and welfare, as well as the validity of experimental results. The use of lower grade substances/compounds with undefined or 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 substances should be used in experimental animals whenever possible, the use of non-pharmaceutical-grade substances 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 substances 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 institutional IACUC

and the use of chemical grade substances must be clearly delineated and justified in the IACUC proposal. Cost savings alone is not considered an adequate justification for the use of non-pharmaceutical-grade substances in laboratory animals.

OLAW has also stated that while the possible implications of the use of non-pharmaceutical grade substances 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.

DEFINITIONS:

1. **Pharmaceutical Grade Substances:** drugs, biologics, or reagents that are 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).
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.

POLICY OUTLINE: This policy is consistent with the guidance from the NIH/ILAR Guide for the Care and Use of Animals, the corresponding Position Statement from AAALAC, International, and the NIH/Office of Laboratory Animal Welfare's Position Statement.

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

1. FDA-approved veterinary or human pharmaceutical substances;
2. FDA-approved veterinary or human pharmaceutical substances used to compound a needed dosage form;
3. USP/NF or BP pharmaceutical grade substance used in a needed dosage form (also includes compounded products from sources such as compounding pharmacies);
4. Analytical grade bulk chemical used to compound a needed dosage form (requires justification);
5. Other grades and sources of substances (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 above.
For a majority of common substances 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:

- Saline
- DMSO
- Corn oil

- Tamoxifen
- Tetracycline
- Analgesics (e.g., buprenorphine)
- Anesthetics (e.g. ketamine)
- Euthanasia reagents (e.g. Euthasol)

When developing and reviewing a proposal to use non-pharmaceutical grade substances, the investigator should consider animal welfare and scientific issues related to the use of the substances, including potential for contamination, safety, efficacy, and the inadvertent introduction of confounding research variables.

For all non-pharmaceutical grade substances used in animals, the IACUC shall 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. The IACUC may use a variety of administrative methods to review and approve the use of such agents. The use of non-pharmaceutical-grade compounds in laboratory animals shall be clearly delineated and justified in the protocol document and/or covered by an IACUC policy developed for their use.

RESPONSIBILITIES:

Investigator:

Investigators are responsible for ensuring that pharmaceutical grade compounds are used whenever they are available. The use of non-pharmaceutical grade anesthetics, analgesics, antibiotics, or euthanasia drugs is especially problematic since the intent of these drugs is to treat potential pain and distress or prevent infection. When pharmaceutical grade compounds are not available the investigator must provide specific details regarding the non-pharmaceutical compound use being proposed and scientific justification for such use. If applicable, as in the case of anesthetics, analgesics, euthanasia compounds, etc., the use of alternative strategies using available pharmaceutical compounds must be addressed. The investigator must also provide sufficient information to the IACUC to permit the IACUC to assess the potential of the non-pharmaceutical grade drug to harm animal health or well-being. This should include specifics regarding the toxicity of the drug components if known, and details regarding the drug preparation where the drug is not a pharmaceutical grade drug and is not compounded by a licensed pharmacist. This should include information regarding the actual drugs used for the preparation (sterility, chemical grade, drug contaminants, etc.), approximate drug pH and osmolality, drug stability and storage, final product sterility, and any quality control procedures used to test the final product.

IACUC:

The IACUC is responsible for evaluating the potential adverse consequences of such agents when used for research. The IACUC should consider the as applicable and relevant to the specific circumstance: 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, storage, and quality control.

Examples for use of Non-Pharmaceutical-Grade Substances: The IACUC may approve the use of non-pharmaceutical-grade substances in the following situations:

1. 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.

2. 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.

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

    • 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.
    • 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.
    • 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.

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

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

REFERENCES:

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

- 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
- NIH Office of Laboratory Animal Welfare: http://grants.nih.gov/grants/olaw/animal_use.htm#non-pharmaceuticalgradecompounds
- Guide for the Care and Use of Laboratory Animals, 8th Edition, 2011.