Guidelines for the Use of Non-Pharmaceutical Grade Compounds in Laboratory Animals

Background: Investigators are expected by regulatory authorities to use pharmaceutical-grade (PG) compounds (PGC) in animals when they are available(1-3). OLAW defines PGCs as, "any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices (GMP) which is approved, conditionally approved, or indexed by the Food and Drug Administration (FDA) or for which a chemical purity standard has been written or established by a recognized compendia [(e.g., United States Pharmacopeia-National Formulary (USP-NF), British Pharmacopeia (BP)]."(1)

When available, PGCs must be used to ensure animal welfare, reliable administration, avoid toxicity or side effects, and support accurate interpretation of research results. Animal Care and Use Committees (ACUCs) may approve the use of nonpharmaceutical grade compounds when scientifically justified. Cost savings alone do not justify the use of non-PGCs. These guidelines will help investigators understand their responsibilities and comply with federal law when the use of non-PGCs is unavoidable. The requirements below also apply to modified pharmaceutical-grade products (i.e., diluted, combined, etc.)(4).

For all compounds administered to animals, the following must be considered in the order presented prior to use; grades 4 and 5 require scientific justification:

1. FDA approved veterinary or human pharmaceutical compounds
    - Approved human PG drugs- Drugs@FDA(5)
    - Approved veterinary PG drugs- Green Book(6)
    - FDA Indexed Drugs- The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species(7)
2. FDA approved veterinary or human PGC used to compound a needed dosage form
3. USP/NF, BP, or other pharmacopeia recognized PGCs used in a needed dosage form
4. Analytical grade bulk chemical (>95% pure)
5. Other grades and sources of compounds

A compound purchased as a product intended for use in medical or veterinary patients is likely PG. A bulk reagent from a chemical supply company, (e.g. 2,2,2-tribromoethanol), or a substance designated for research use only, is most likely NOT PG. If you are unsure, please consult your institute veterinarian.

It is critical that investigators provide sufficient information in an Animal Study Proposal (ASP) for all substances administered to live animals for the ACUC to effectively evaluate safety. The inclusion of the table below may facilitate ACUC assessment:

Compound Name	PG grade? (Yes or no)	Grade, if not PG?	Route	Sterile?	Neutral pH and isotonic?

Additionally:

a) For non-PGCs scientifically justify why a PGC cannot be used. Examples of acceptable scientific justifications for the use of non-PGCs(1) include:
    - A PGC is not available.

- A PGC is not available in the appropriate concentration or formulation, or the appropriate vehicle control is unavailable.
- A PGC is not available for the specified route of delivery.
- The non-PGC is required to generate data comparable to previous work.

b) If the compound will be diluted, mixed, suspended, dissolved, or mixed into the animal's drinking water or food, or otherwise altered, describe what will take place.

c) Describe the solvent/vehicle to be used and final concentration(8, 9). Diluents, excipients, or vehicles administered to animals should be PG, if available. Products administered orally, which are not PG, should be food-grade.

d) Ensure the pH and tonicity of the final product to be administered are appropriate for the route of administration.

e) Compounds delivered parenterally must be sterile(10), unless scientifically justified. Orally or topically delivered substances do not require sterilization. If the compound cannot be sterilized, provide a scientific justification and describe what techniques will be used to ensure the final product is free of unwanted pathogens, pyrogens (such as endotoxin) or contaminants that might impact animal welfare. The two most used sterilization techniques are autoclaving and filter sterilization (0.22-micron pore or smaller). Aseptic technique in the preparation of all compounds is critical.(11)

ACUCs should prioritize the health and well-being of the animals when the use of non-PGCs are unavoidable, while aiding researchers in minimizing potentially confounding experimental variables and maximizing reproducibility of the research.(2) ACUCs should consider whether the chemical properties of the compound are appropriate for the study and the route of administration (e.g., purity, grade, sterility, stability in and out of solution, solution vehicle properties, pH, osmolality, pyrogenicity and compatibility of the solvent and other components of final preparation).(2, 8, 9) The method of preparation, labeling, administration, and storage of formulations should aim to maintain their stability and quality.

References:

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