WVU IACUC POLICY:
Non-Pharmaceutical-Grade Substances Used in Animals

Purpose

This policy describes the expectations of the WVU Animal Care and Use Committee (IACUC) when non-pharmaceutical-grade substances are administered to animals used in research, training, or teaching. The IACUC recognizes that some animal use protocols involve the administration of experimental or proprietary compounds that are not available in pharmaceutical grade. In these cases, the principal investigator (PI) is responsible for justifying their use and minimizing potential adverse effects. Background information can be found in the Resources section at the end of this policy.

Definitions

Pharmaceutical grade: 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) or British Pharmacopeia (BP).

Analytical grade bulk chemical: ~99% purity; certificate of analysis is usually available.

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.

- USP-grade reagents/chemicals from chemical companies that state they are only meant for test and assay use and are not meant for administration to humans and animals cannot be considered pharmaceutical grade.

BP: British Pharmacopeia

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

Compounding: the customized manipulation of an FDA-approved drug beyond what is stipulated on its product label

Clinical Use: Compounds used for the clinical treatment of animals and to prevent or reduce/eliminate animal pain or distress. Whenever possible, pharmaceutical-grade compounds ***must*** be used. (AAALAC FAQ)

Research Use: Compounds used to accomplish the scientific aims of the study. If available, and suitable, pharmaceutical-grade compounds are preferred; but when non-pharmaceutical-grade preparations are used, AAALAC International will expect investigators and the IACUC (or comparable oversight body) to consider the following factors:

- Use ***must*** be compliant with applicable national or regional regulatory guidelines and requirements and the requirements of relevant funding agencies;

- A scientific justification is provided;
- The pharmaceutical-grade compound is not available in the appropriate concentration or formulation or the appropriate vehicle control is unavailable.
- The compound is required to generate data that are part of an ongoing study or that are comparable to previous work.
- The chemical properties of the compound are appropriate for the study and the route of administration (e.g., the purity, grade, stability in and out of solution, solution vehicle properties, pH, osmolality, and compatibility of the solvent and other components of final preparation). In some cases, the reagent-grade of the compound may be as or purer than the pharmaceutical-grade.
- The method of preparation, labeling (i.e., preparation and use-by dates), administration and storage of formulations should be appropriately considered with the aim of maintaining their stability and quality (i.e., to prevent inadvertent co-administration of infectious agents or contaminants).

Acceptable Scientific Reasons for Non-Pharmaceutical-grade drug use (not a complete list):

- Compound is not available in a veterinary or human pharmaceutical-grade formulation.
- Commercially available veterinary or human drug formulation is available, but it does not meet study needs (not appropriate for route of administration, concentration not consistent with dosing needs, preservatives/inactive ingredients/vehicles included cannot be used in study).
- Commercially available veterinary or human drug formulation is available; however, this formulation cannot be used in order to replicate methods from a previous study because results are directly compared with those previous studies.

Policy

A. When selecting compounds, the following order of choice should be applied:
   - FDA-approved veterinary or human pharmaceutical substances
   - FDA-approved veterinary or human pharmaceutical substances obtained from a compounding pharmacy for a needed concentration, dosage form, or formulation
   - USP/NF- or BP-pharmaceutical-grade substance used in a needed dosage form
   - Analytical grade bulk chemical/reagents used to compound a needed dosage form
   - Other grades and sources of substances

B. The use of non-pharmaceutical-grade compounds ***must*** be justified and approved by the IACUC prior to their use in live animals.
   - Any compound administered to a live animal should be pharmaceutical-grade, if available.
   - If pharmaceutical-grade is not available or cannot be used for a scientific reason, the highest degree of purity available should be used.
   - One exception is non-pharmaceutical-grade pentobarbital, which is currently approved for use in animals due to the limited availability and exorbitant cost of pharmaceutical-grade pentobarbital.
   - Other exceptions should be considered by the IACUC on a case-by-case basis, as needed.

C. The IACUC protocol application should include the following information for each non-pharmaceutical-grade compound:
   - Scientific justification for its use.
   - Any available information on grade, source, purity, sterility, pH, pyrogenicity, osmolality, stability

of the compound.

- Sterility
  - The compound ***must*** be sterilized before parenteral administration to an animal, unless justified.
  - Method of sterilization ***must*** be described in the IACUC protocol.
  - Common methods used include 0.22 micron filtration of compounded drug or autoclave sterilization. If autoclave sterilization is utilized the compound concentration, safety and efficacy ***must not*** be altered by the process.
  - Aseptic technique is necessary when compounding drugs in the lab.
- pH
  - pH should be described when final product is not neutral.
  - If necessary, buffering procedure should be described.
- Stability/Storage (see multi-dose and mixed-substance container labeling used and expiration date policy)
  - Storage conditions ***must*** be acceptable to protect compound efficacy, purity, sterility, and stability. Considerations include appropriate temperature, exposure to light, exposure to humidity, vehicles, composition of storage container, etc.
  - Novel compounds may not have data regarding stability, storage conditions and expiration date. A pilot study would need to be performed to validate this information or compound made fresh prior to each use.

- Vehicles
  - Diluents, excipients, or vehicles should be pharmaceutical grade when available and listed in the IACUC protocol.
  - Potential toxicity and adverse outcomes of vehicles ***must*** be considered.
  - If non-pharmaceutical grade compounds are used for this purpose they ***must*** be justified in the IACUC protocol.
  - Veterinary and human drugs that are reconstituted in a manner not in accord with the product insert are considered non-Pharmaceutical Grade Compounds.
  - If the compound is administered orally, food-grade products should be used when possible. If food grade is not used describe in the IACUC protocol.
- Describe dose, site, and route of administration.
- Describe formulation, preparation process, compatibility, and pharmacokinetics of the compound, if available.
- Describe the potential for side effects & adverse reactions in animals. Include how animals will be monitored to detect these events and what, if any, treatments may be required.
- For food-animal species (agricultural and wildlife) use of non-pharmaceutical grade compounds could cause them to be considered adulterated and not able to enter the food supply. All substances administered to animals should be listed in the animal use protocol. Any substances administered orally are expected to be food-grade substances. If food-grade substance is not available, that should be described and justified in the protocol. AV and IACUC office should be consulted regarding if approval from an outside agency is available. See *IACUC Policy: Residue Avoidance in Research Using Food-producing Agricultural Animals*.

Resources/Regulations

According to the *Guide for the Care and Use of Laboratory Animals*, 8th ed (p31): "The use of pharmaceutical-grade chemicals and other substances ensures that toxic or unwanted side effects are not

introduced into studies conducted with experimental animals. They should therefore be used, when available, for all animal-related procedures (USDA 1997b). The use of non-pharmaceutical-grade chemicals or substances should be described and justified in the animal use protocol and be approved by the IACUC." https://grants.nih.gov/grants/olaw/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf

According to the *Guide for the Care and Use of Agricultural Animals in Research and Teaching*, administration of drugs to animals destined to enter the food chain requires special consideration. Before an animal may be slaughtered for human or animal food purposes, time ***must*** be allowed for medications, drugs approved by the Food and Drug Administration (FDA), or substances allowed by the FDA for experimental testing under the Investigational New Animal Drug (INAD) exemption to be depleted from the tissues.
https://www.asas.org/docs/default-source/default-document-library/agguide_4th.pdf?sfvrsn=56b44ed1_2

OLAW and USDA agree that pharmaceutical-grade substances, when available, ***must*** be used to avoid toxicity or side effects that may threaten the health and welfare of vertebrate animals and / or interfere with the interpretation of research results. Procedures that may cause more than momentary or slight pain or distress to animals ***must*** be relieved by sedation, analgesia, or anesthesia using veterinary or human pharmaceutical-grade substances, unless the use of a non-pharmaceutical-grade substance is scientifically necessary, appropriately justified, and approved by the IACUC. The use of a non-pharmaceutical-grade euthanasia agent ***must*** meet the same criteria.
(OLAW FAQ: https://olaw.nih.gov/faqs#/guidance/faqs?anchor=50361)

According to the *USDA Animal Care Policy Manual*, 2016 (p3.2): "Pharmaceutical-grade substances are expected to be used whenever they are available, even in acute procedures. Non-pharmaceutical-grade substances should only be used in regulated animals after specific review and approval by the IACUC. The IACUC should develop a consistent evaluation process that includes, but is not limited to, the scientific justification and the availability of an acceptable veterinary or human pharmaceutical-grade product. Cost savings alone is not sufficient justification for using a non-pharmaceutical-grade substance in regulated species, however, unavailability or shortages of pharmaceutical grade substances may lead to cost increases, and the IACUC may determine that this justifies the use of the non-pharmaceutical-grade substitution.
https://animal.research.wvu.edu/files/d/8e972269-0c20-4984-8cc2-e195b9cd4ef4/animal-care-policy-manual.pdf

Guidelines for the Use of Non-Pharmaceutical Grade Compounds in Laboratory Animals (NIH)
https://oacu.oir.nih.gov/system/files/media/file/2023-05/b14_pharmaceutical_compounds.pdf