POLICY

Pharmaceutical-grade agents are to be used whenever they are available, even in acute procedures. The use of non-pharmaceutical grade agents in laboratory animals under certain circumstances may be a necessary and acceptable component of biomedical research.

In the event that a non-pharmaceutical grade agent has to be used due to (1) scientific necessity and/or (2) non-availability of a veterinary or human pharmaceutical grade compound, specific review and approval by the IACUC is required. Cost savings alone is not an adequate justification for using non-pharmaceutical grade agents.

In addition to strong justification for the need to use non-pharmaceutical grade agents, the method of preparation of the drug, means to ensure sterility and biocompatibility, and storage conditions must be described in the IACUC protocol. In particular, it is expected that the procedures and criteria described in this policy are followed when preparing and storing agents intended for administration to animals. Exceptions may be granted for compounding of the final preparation used for oral gavage or administered in food or drinking water.

Definitions:

• Pharmaceutical grade agents: A drug, biologic, reagent etc. which is approved by the Food and Drug Administration (FDA) or for which a chemical purity standard has been written/established by United States Pharmacopeia (USP), National Formulary (NF), European Pharmacopeia (Ph. Eur), or British Pharmacopeia (BP).

REGULATION

Reference 9CFR Animal Health and Husbandry Standards, 3.110 Veterinary Care, USDA Animal Care Resource Guide Policies, March 25, 2011, Policy #3 Veterinary Care:
Investigators are expected to use pharmaceutical-grade medications whenever they are available, even in acute procedures. Non-pharmaceutical-grade chemical compounds should only be used in regulated animals after specific review and approval by the IACUC for reasons such as scientific necessity or non-availability of an acceptable veterinary or human pharmaceutical-grade product. Cost savings is not a justification for using non-pharmaceutical grade compounds in regulated animals.

Guide for the Care of and Use of Laboratory Animals, ILAR, NAS, Eighth Edition 2011, pg 31: 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 (Wolff et al. 2003).

PROCEDURE
1.0 The following questions should be considered when deciding what formulation of agent to use:

2.0 When developing and reviewing a proposal to use non-pharmaceutical grade agents and/or investigational drugs where the grade and formulation is not known the Investigator and the IACUC should consider the following:

2.1 Animal welfare and scientific issues related to the use of the agent(s).

2.2 Potential for contamination, safety, efficacy, and the introduction of research variables.

3.0 For all agents, the Investigator and the IACUC should consider the following:

3.1 The grade of the chemical being proposed (i.e. how pure the agent is).

- **A.C.S.** - A chemical grade of highest purity and meets or exceeds purity standards set by American Chemical Society (ACS).
- **Reagent** - High purity generally equal to A.C.S. grade and suitable for use in many laboratory and analytical applications.
- **Lab** - A chemical grade of relatively high quality with exact levels of impurities unknown; usually pure enough for educational applications. Not pure enough to be offered for food, drug, or medicinal use of any kind.
- **Purified** - Also called pure or practical grade, and indicates good quality chemicals meeting no official standard; can be used in most cases for educational applications. Not pure enough to be offered for food, drug, or medicinal use of any kind.
- **Technical** - Good quality chemical grade used for commercial and industrial purposes.
Not pure enough to be offered for food, drug, or medicinal use of any kind.

3.2 Issues related to sterility, pyrogenicity, stability, pH, osmolality, site/route of administration, pharmacokinetics, physiological compatibility, and quality control.

3.3 The formulation of the final product.

4.0 Reconstituting or diluting agents to be administered to animals.

4.1 When reconstituting or diluting agents to be administered to animals, it must be performed in a clean/sanitary environment with a method to sterilize the final preparation.
- Clean/sanitary work space (Safety cabinet or chemical fume hood when required)
- Disposable latex or nitrile gloves
- Sterile diluent/vehicle/solvent
- Sterile syringes
- Sterile storage containers/vials with stoppers that provide elastomeric closure to prevent pathogen entry are required for injectables.
- For agents to be administered orally ensure that they are stored in containers that prevent microbial contamination.

4.2 Where possible agents and diluents/vehicles/solvents should be passed through a syringe filter (0.22 um or finer).
- This can be done when transferring to a sterile injection vial/container.
- If there is any question about the sterility of a stored solution, it should also be filtered at the time of use.
- If filtering is not possible (e.g., nanoparticles) alternative methods of sterilization must be described or justification of the need to use non-sterile agent must be provided.

4.3 Diluents/vehicles/solvents must be specified in the animal use protocol. The diluent/vehicle solvent will be evaluated based on toxicity to animals, compatibility with agents, and volume/route of administration.
- See a list of common diluents/vehicles/solvents in Section 4.11.

4.4 The pH of the final preparation must be checked and should be between pH 4.5 and 8.0.
- Use of a solution with a pH outside this range must be reviewed by the IACUC and may not be approved if considered potentially toxic and/or painful to the animal.

4.5 The Osmolality of the final preparation should be isotonic, (around 300 mOsm/kg) whenever possible.
- Non-isotonic formulations may either cause red blood cell crenation or haemolysis when administered via the intravenous route, or may cause localized tissue damage and associated pain upon injection.
- Non-isotonic formulations should be administered slowly and in small volume.

4.6 Storage container/vials must be labeled with the agent, concentration, and expiration date and mix date.
- When no expiration date is available, mix date is required and length of time that agent can be maintained must be based on known efficacy.

4.7 Prepare only as much as can be used in a reasonable period of time.
- Agents must be stored properly with consideration for chemical properties and according to manufacturer or similar commercial product recommendations. (e.g., freezer, refrigerator, etc.).
- Agents must not be used if they are cloudy, discolored, precipitated, etc.

4.8 You should keep a written record of preparation of agents and administration of final preparation to animals.

4.9 Some agents may have been tested for pyrogens, such as endotoxins. Check the source of the agent for information to see if pyrogen testing has been performed.
- Pyrogens, such as endotoxins may cause fever when injected into an animal.
- Sterility does not assure that pyrogens are not present.
• Filtering does not remove pyrogens.
• Pyrogen testing is not practical for small lots of prepared agent.
• Pyrogenicity is a potential experimental variable that researchers should be aware of when using non-pharmaceutical grade agents.

4.10 Consideration should always be given to conducting a Pilot Study, and based on the information provided about the agent the IACUC may request one to be completed.
  • If a novel agent is being tested, a pilot study using a minimum number of animals should be conducted to determine the dose and potential adverse effects. This would in turn help determine humane end point criteria specific to the project.

4.11 Common vehicle/diluents/solvents:
  • Sterile water
  • Physiological Salt Solution (e.g., 0.9% NaCl), PBS, balanced salt solution (e.g., Hanks)
  • 60% (v/v) propane-1:2-diol (propylene glycol)
  • 0.5% (w/v) carboxymethyl cellulose
  • 10% (v/v) Tween 80 (polyoxyethylene (20) sorbitan mono-oleate)
  • 10% (v/v) ethyl alcohol
  • 50% (v/v) dimethylformamide
  • 50% (v/v) dimethylsulfoxide (DMSO)
  • Cyclodextrins5 (e.g. 2-hydroxypropyl-beta-cyclodextrin, Trappsol ®)
  • Food/Diet

5.0 For more information on drug procurement, storage, disposal, controlled drugs and record keeping please see **Policy for Management of Pharmaceuticals**.