

Guidelines for the Use of Non-Pharmaceutical Grade Compounds

A pharmaceutical grade compound is a drug, biologic, reagent, etc. which is approved by the Food and Drug Administration (FDA), manufactured in compliance with the FDA Good Manufacturing Practices (GMP) guidelines and for which a chemical purity standard has been written/established by United States Pharmacopeia/National Formulary (USP/NF) or British Pharmacopeia (BP). The use of non-pharmaceutical grade chemical compounds in experimental animals under certain circumstances has been, and will continue to be, a necessary and acceptable component of biomedical research. The NIH Office of Laboratory Animal Welfare (OLAW) and United States Department of Agriculture (USDA) have determined that their use should be based upon (1) scientific necessity, (2) non availability of an acceptable veterinary or human pharmaceutical-grade compound, and (3) specific review and approval by the ACUC.¹

The use of materials that meet documentable standards of purity and composition ensures that reliable, reproducible compounds are used in preclinical research which in turn helps ensure research animal health and welfare, as well as the validity of experimental results. By definition, analytic and reagent ACS grade chemicals are >95% pure and thus are of a grade comparable to many pharmaceutical grade chemicals as defined by USP/NF. Although sterility, pyrogenicity, stability, and manufacturing quality control are addressed during GMP production of pharmaceuticals, the same is not true for non-GMP grade chemicals. However, the use of non-GMP compounds in experimental animals can be an acceptable practice, and in many preclinical settings, it is a required practice. While use of GMP-grade compounds is recommended, non-GMP grade chemicals may be used when approved by the ACUC under the conditions outlined below.

Recommendations for Use:

When developing and reviewing a proposal to use non-GMP grade compounds, the Principal Investigator and ACUC should consider a number of related animal welfare and scientific issues including safety, efficacy, and the inadvertent introduction of research-complicating variables. Justification for their use in the Animal Study Proposal should include details on the scientific merit for use of a non-pharmaceutical-grade chemical compound. Cost savings alone do not adequately justify the use of non-pharmaceutical-grade compounds in animals.

For all chemicals used, the ACUC should 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.

For pharmaceutical grade compounds requiring a prescription, please contact the LAM veterinary staff for assistance in purchasing these items.

Non-GMP grade compounds

- 1) The use of non-GMP grade compounds must be approved by the ACUC, based on scientific justification for its use.

- Some examples of scientific justification include:
 - 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 a part of an ongoing study or that are comparable to previous work
 - The chemical properties of the compound may be more appropriate for the study and route of administration. In some cases, the reagent-grade of the compound may be as or more pure than the pharmaceutical grade
- 2) The use of non-GMP compounds must be compliant with application federal and state regulations and requirements of the relevant funding agency
- 3) Non-pharmaceutical grade compounds can be used if evaluated and approved by the ACUC, with a statement in the protocol that the animals will be monitored for adverse effects.
- 4) When working with non-GMP grade compounds, monitoring must be provided to insure that animals remain healthy, and that any signs of toxicity are detected early. Such monitoring should include an ACUC approved plan to deal with any known toxicity.
- 5) Must be clearly labeled with compound concentrations and date of preparation. Since shelf-life of such compounds is unknown, long-term storage (>30 days) is strongly discouraged. Regardless of age, solutions should be discarded if changes in color and/or precipitation occur.
- 6) Should be documented regarding safety and efficacy consistent with methods of successful use/efficacy in published scientific literature, if available. In addition, body weights, clinical signs (hunched, inactive, reduced appetite, etc), and unexpected events should be monitored for all compound use and LAM should be notified if unexpected events occur. The plan for resolving toxicity-related issues should be provided in the ACUC protocol (humane euthanasia, contacting LAM).
- 7) Investigators will ensure that any chemical material prepared for administration to research animals is prepared and maintained under sterile conditions regardless of its GMP status. This may be accomplished by multiple methods (e.g., prepare using sterile technique, sterile filtration of test material) and the PI should provide the proposed approach(es) in the ACUC protocol.
 - This includes storage in an endotoxin-free sterile vial with a sealed top appropriate for repeated needle insertion, if the route of administration will be by injection
- 8) May be used due to lack of availability of higher grade compounds as occurs with new chemical entities.

References:

¹ NIH Office of Laboratory Animal Welfare:
http://grants.nih.gov/grants/olaw/animal_use.htm#non-pharmaceuticalgradecompounds

AAALAC Frequently Asked Questions:
http://www.aaalac.org/accreditation/faq_landing.cfm#B9