

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

Investigators are expected by regulatory authorities to use pharmaceutical grade compounds whenever possible. The Guidelines presented here are a synopsis of the requirements and expectations for the use of non-pharmaceutical-grade compounds (Non-PGCs) when they are necessary. This document references the policies and guidelines of the major animal research oversight organizations.¹⁻⁶

Definitions:

Pharmaceutical-grade compound: A pharmaceutical-grade compound (PGC) is defined as any active or inactive drug, biologic or reagent, for which a chemical purity standard has been established by a recognized national or regional pharmacopeia (e.g., the U.S. Pharmacopeia (USP), British Pharmacopeia (BP), National Formulary (NF), European Pharmacopoeia (EP), Japanese Pharmacopeia (JP), etc.). These standards are used by manufacturers to help ensure the products are of the appropriate chemical purity and quality, in the appropriate solution or compound, to ensure stability, safety, and efficacy.² The Food and Drug Administration (FDA) maintains a database listing of FDA approved commercial formulations for both FDA approved human drugs (the [Orange Book](#)) and veterinary drugs (the [Green Book](#)).

Availability: Refers to compounds that are commercially available from an active U.S. vendor.

New investigational compound: A compound supplied by its manufacturer for testing in an experimental setting only and for this reason would not have chemical purity standards established and by default is considered a non-pharmaceutical-grade compound.

Requirements:

When compounds are used for the clinical treatment of animals or to prevent or reduce/eliminate animal pain or distress, PGCs must be used whenever possible.²

When compounds are used to accomplish the scientific aims of the study PGCs are preferred if available and suitable.²

The use of Non-PGCs in laboratory animals must be described and justified in the Animal Study Proposal and/or covered by an Institute/Center Animal Care and Use Committee (IC ACUC) policy developed for their use and approved by the IC ACUC.

AAALAC states that the investigator and the IC ACUC consider the following factors when using Non-PGCs:²

- The provided scientific justification such as:
 - A PGC is not available; this includes new investigational compounds.
 - A PGC is not available in the appropriate concentration or formulation or the appropriate vehicle control is unavailable.
 - The Non-PGC is required to generate data that are part of an ongoing study or to generate data that are comparable to previous work.
- Whether 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).
- The method of preparation, labeling (preparation and use-by dates), administration and storage of formulations should be appropriately considered with the aim of maintaining their stability and quality.
- Use must be compliant with applicable national or regional regulatory guidelines and requirements and the requirements of relevant funding agencies.

The last three factors are not specific to Non-PGCs and therefore should be considered by the IC ACUC in general terms as is done for all pharmaceuticals and reagents.

Although the potential animal welfare consequences of complications are less evident in non-survival studies, the scientific issues remain the same as in survival studies and therefore apply to non-survival studies. The use of a non-pharmaceutical-grade euthanasia agent must meet the same standards as for use in any other application.³

The guidelines pertain 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. Veterinary and human drugs that are reconstituted in a manner not in accord with the product insert are considered Non-PGCs.

Recommendations for use of non-pharmaceutical-grade compounds:

Where the use of Non-PGCs may be essential for the conduct of science, the goal of the IC ACUC should be to consider the health and well-being of the animals while aiding the researcher in minimizing potentially confounding experimental variables and maximizing reproducibility of the research.²

As stated by Office of Laboratory Animal Welfare, this Guideline suggests that the IC ACUC, in making its evaluation may consider factors including, for example grade, purity, sterility, acid-base balance, pyrogenicity, osmolality, stability, site and route of administration, compatibility of components, side effects and adverse reactions, storage, and pharmacokinetics.³ The following should be considered in the order presented for pharmaceuticals and reagents of all kinds prior to use:

1. FDA approved veterinary or human pharmaceutical compounds;
2. FDA approved veterinary or human pharmaceutical compounds 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 used to compound a needed dosage form (requires justification);
5. Other grades and sources of compounds (requires justification).

The [NIH Veterinary Pharmacist](#) can provide assistance in availability, procurement, and formulation of various PGCs.

The IC ACUC may use a variety of administrative methods to review and approve the use of such agents. For example, the IC ACUC may establish acceptable scientific criteria within the institution, rather than on a case-by-case basis. Investigators and IC ACUCs should consider relevant animal welfare and scientific issues including safety, efficacy, availability of PGCs, and the inadvertent introduction of new variables.³ Cost savings alone is not an adequate justification for the use of Non-PGCs. However, unavailability or shortages of PGCs may lead to

cost increases and necessitate that the IC ACUC determine whether this justifies the use of the Non-PGC substitution.⁶

Acceptable scientific justifications for the use of non-pharmaceutical-grade compounds:⁴

1. No equivalent veterinary or human drug is available for experimental use. The highest-grade equivalent chemical reagent should be used and formulated aseptically, 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 analytical or chemical grade reagent may be required to replicate methods from previous studies if it is the only option to produce results that are directly comparable.
3. Although an equivalent veterinary or human drug is available, dilution or change in formulation is required.
 - If the formulation as provided must be diluted, altered by addition, or otherwise changed, there may be no additional advantage to be gained by using the USP formulation.
 - In this situation, 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 administration.

References:

1. U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care, Animal Care Policy Manual, [Policy #3 Veterinary Care](#), March 14, 2014.
2. AAALAC [Frequently Asked Questions: C. Institutional Responsibilities 9. Non-Pharmaceutical-Grade Compounds](#)
3. OLAW [Position Statement- Non-Pharmaceutical-Grade Substances](#)
4. Transcript of OLAW [On-line Seminar broadcast on March 1, 2012](#) - Use of Non-Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals
5. Transcript of OLAW [On-line Seminar broadcast on June 4, 2015](#) - Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals
6. OLAW [Frequently Asked Questions – PHS Policy on Humane Care and Use of Laboratory Animals, F. Animal Use and Management, 4. May investigators use non-pharmaceutical-grade substances in animals?](#)

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