

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

As part of our AAALAC International accreditation, investigators are expected to use pharmaceutical grade compounds whenever possible during their research involving animals.

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 Chinese Pharmacopeia (ChP), 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.¹

Availability: Refers to compounds that are commercially available from an active Hong Kong 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.²

Requirements: AAALAC distinguishes between two scenarios when considering the use of non-pharmaceutical-grade compounds:

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.

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 CULATR 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 more pure than the pharmaceutical-grade; and

- The method of preparation, labelling (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).¹

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.²

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.

CULATR Policy on the use of non-pharmaceutical-grade compounds

The use of non-pharmaceutical-grade compounds in the following listed situations will be considered by CULATR to be scientifically justified, and not requiring further CULATR review:

1. No equivalent or alternative veterinary or human drug is available for experimental use. The highest- grade equivalent chemical reagent will 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.
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.

In the CULATR Protocol form, the investigator will be required to declare that each non-pharmaceutical-grade compound being used meets at least one of these scientific justification criteria. Any compound to be used that does not fall within the described scientific justifications must seek CULATR approval on a case by case basis in accordance with the following principles:

Where the use of Non-PGCs may be essential for the conduct of science, the goal of the CULATR 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.¹

AAALAC International acknowledges that in an animal care and use program, non-pharmaceutical-grade compounds often are necessary for scientific research. Where the use of non-pharmaceutical-grade substances may be essential for the conduct of science, the goal of the CULATR 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. The Council on Accreditation will apply a performance approach to its assessment of the use of non-pharmaceutical-grade compounds, and will expect that the CULATR has established acceptable criteria for use of such

compounds within the institution and for review and approval of their use. The CULATR, 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.¹

The following should be considered in the order presented for pharmaceuticals and reagents of all kinds prior to use:

1. Hong Kong Registered/Approved veterinary or human pharmaceutical compounds;
2. Other International pharmacopeia recognized PGCs used in a needed dosage form;
3. Analytical grade bulk chemical used to compound a needed dosage form (requires justification);
4. Other grades and sources of compounds (requires justification).

Investigators and CULATRs should consider relevant animal welfare and scientific issues including safety, efficacy, availability of PGCs, and the inadvertent introduction of new variables. 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 CULATR determine whether this justifies the use of the Non-PGC substitution.²

References:

1. AAALAC Frequently Asked Questions: C. Institutional Responsibilities 9. Non- Pharmaceutical-Grade Compounds: https://www.aaalac.org/accreditation/faq_landing.cfm#B9
2. NIH Office of Animal Care and Use: https://oacu.oir.nih.gov/sites/default/files/uploads/arac-guidelines/pharmaceutical_compounds.pdf