Institutional Animal Care and Use Committee

Effective Date: July 2017
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Next review date: April 2024

Policy:	Use of Pharmaceutical Grade Compounds in Laboratory Animals
Purpose:	To provide standard for pharmaceutical grade compounds and justification requirement for all non-pharmaceutical grade compound use
Applicable To:	UMass Boston Research Community

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 major animal research oversight organizations.

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. 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 considered a non-pharmaceutical grade compound.

Requirements:

Pharmaceutical-grade substances are expected to be used whenever they are available, even in acute procedures. This includes but is not limited to compounds, medications, drugs, vehicles, and diluents. 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 which includes but is not limited to the scientific justification and the availability of an acceptable veterinary or human pharmaceutical-grade product.

Evaluation Plan:

When compounds are used for the clinical treatment of animals or to prevent /reduce or eliminate pain or distress, PGCs must be used whenever possible. When compounds are used to accomplish the scientific aims of the study PGCs are preferred if available and suitable. The use of Non-PGCs in laboratory animals must be described and scientifically justified in the animal care and use protocol. AAALAC states that the investigator and the IACUC consider the following factors when using Non-PGCs:

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

1. No equivalent or 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, dilution or change in formulation is required.
    - If the formulation as provided must be diluted, altered by addition, or otherwise changed, there maybe 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 judgement should be used to determine the appropriate test material and to ensure use of an agent with the least likelihood for causing adverse effects.
3. The available human or veterinary drug is not concentrated enough to meet experimental requirements.
4. The available human or veterinary drug does not meet the non-toxic vehicle requirements for the specified route of administration.

Other considerations that should be addressed in the protocol for the use of PCG and Non-PCG compounds include:

- 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 of the compound(s) must be compliant with applicable national or regional regulatory guidelines and requirements and the requirements of relevant funding agencies.

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.

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 IACUC 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.

As stated by Office of Laboratory Animal Welfare, this Guideline suggests that the IACUC, 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.

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).

Investigators and IACUC should consider relevant animal welfare and scientific issues including safety, efficacy, availability of PGCs, and the inadvertent introduction of new variables.

Cost saving 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 IACUC determine whether this justifies the use of the Non-PGC substitution.

References:

1. NIH Section F. 4; Frequently Asked Questions | OLAW (nih.gov)

2. Office of Laboratory Animal Welfare - Adoption of the Guide for the Care and Use of Laboratory Animals: Eighth Edition (nih.gov) (note this is an archived link and some content may have expired or links within might be broken—for reference only)

3. Transcript of OLAW On-line Seminar broadcast on June 4, 2015 - Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals

4. AAALAC International, Section C. 9 FAQs - AAALAC