



**Division of Research**

<b>SUBJECT:</b> Use of Non-Pharmaceutical Grade Substances in Laboratory Animals	<b>Effective Date:</b> 10/25/2019	<b>Policy Number:</b> 10.4.25	
	<b>Supersedes:</b> 10/28/2016 10/25/2013	<b>Page</b> <b>1</b>	<b>Of</b> <b>4</b>
	<b>Responsible Authorities:</b> Vice President, Research Institutional Animal Care and Use Committee Assistant Vice President for Research Integrity Assistant Vice President for Comparative Medicine Principal Investigator		

- I. Background  
The use of pharmaceutical-grade substances in laboratory animals ensures that the substances administered meet established documentable standards of purity and composition. This in turn helps ensure research animal health and welfare, as well as the validity of experimental results. The use of lower grade substances/compounds with undefined or higher levels of impurities or poorly formulated non-commercial preparations can introduce unwanted experimental variables or even toxic effects, and so should be avoided if at all possible.
  
- II. Purpose  
To comply with the Office of Laboratory Animal Welfare (OLAW) and United States Department of Agriculture (USDA) regarding their Guidelines for the use of non-pharmaceutical grade substances in laboratory animals.
  
- III. General Statement  
Although pharmaceutical grade substances should be used in experimental animals whenever possible, the use of non-pharmaceutical-grade substances in experimental animals is an acceptable practice under certain circumstances. For example, in the case of new investigational compounds, they would be the only grade and formulation available. The NIH Office of Laboratory Animal Welfare (OLAW) and the United States Department of Agriculture (USDA) both have determined that the use of non-pharmaceutical-grade substances should be based on (1) scientific necessity, (2) non-availability of an acceptable veterinary or human pharmaceutical-grade compound, and (3) specific review and approval by the IACUC. Cost savings alone is not considered an adequate justification for the use of non-pharmaceutical-grade substances in laboratory animals. OLAW has also stated that while the possible implications of the use of non-pharmaceutical grade substances in non-survival studies appears less evident, the scientific issues remain the

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same and professional judgment, as outlined above, must still apply. It is important to understand that OLAW's statement pertains 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.

#### IV. Policy

For all compound use, the IACUC 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.

When selecting compounds the following order of choice should be applied:

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 or BP pharmaceutical grade compound 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).

NOTE: For new investigational drugs the grade and formulation is not optional, but the investigator and IACUC can verify health and safety issues described above.

NOTE: When developing and reviewing a proposal to use non-pharmaceutical grade compounds the investigator and IACUC should consider animal welfare and scientific issues related to the use of the compounds, including potential for contamination, safety, efficacy, and the inadvertent introduction of confounding research variables.

**For all non-pharmaceutical grade substances used in animals, the IACUC shall 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.**

The IACUC may use a variety of administrative methods to review and approve the use of such agents. For example, the IACUC may establish acceptable scientific criteria within the institution, rather than on a case-by-case basis. The use of non-pharmaceutical-grade compounds in laboratory animals shall be clearly delineated and justified in the protocol document and/or covered by an IACUC policy developed for their use.

**Examples for use of Non-Pharmaceutical-Grade Substances:** It would be reasonable for the IACUC to review and the Committee may approve the use of non-pharmaceutical-grade substances in the following situations:

- a. If no equivalent veterinary or human drug is available for experimental use, then the highest-grade equivalent chemical reagent should be used and formulated aseptically and with a non-toxic vehicle as appropriate for the route of administration.
- b. Although an equivalent veterinary or human drug is available for experimental use, the chemical-grade reagent is required to replicate methods from previous studies because results are directly compared to those of replicated studies.
- c. Although an equivalent veterinary or human drug is available, dilution or change in formulation is required.

- Dilution of a pharmaceutical grade substance with a non-pharmaceutical grade substance results in the original compound no longer being pharmaceutical grade. Therefore, if adulteration by dilution, addition or other change in formulation is required, there may be no additional advantage to be gained by using the USP formulation
  - 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.
- d. The available human or veterinary drug is not concentrated enough to meet experimental requirements.
- e. The available human or veterinary drug does not meet the non-toxic vehicle requirements for the specified route of injection.
- f. The human or veterinary drug contains preservatives or other additives that interfere with the research being conducted and subsequent outcome of the study.

V. Definitions

1. **Pharmaceutical grade compound:** Drug, biologic, reagent, etc. which is approved by the FDA or for which a chemical purity standard has been written/established by USP/NF, BP
2. **Analytical grade bulk chemical:** ~99% purity; Certificate of Analysis is usually available
3. **Non-availability:** Not commercially available from an active US vendor; includes formulations supplied as tablet, capsule, injectable, etc.
4. **Investigational compound:** Supplied by its manufacturer for testing in an experimental setting only and for this reason would not have chemical purity standards established; by default is considered a non-pharmaceutical grade compound
5. **USP/NF:** United States Pharmacopeia/National Formulary
6. **BP:** British Pharmacopeia
7. **FDA:** Food and Drug Administration; FDA approved compounds are manufactured using USP/NF compounds

VI. Accountability

**The Principal Investigator (PI) will be responsible for:**

- Assuring that pharmaceutical grade substances will be used in all studies unless otherwise approved with appropriate justification by the IACUC
- Assuring that every effort has been made to find a pharmaceutical grade compound before petitioning the IACUC for approval of use of a non-pharmaceutical grade compound in or on an animal.

**The IACUC will be responsible for:**

- Reviewing and approving, requiring modifications in (to secure approval) or withholding approval of IACUC protocols and/or amendments, especially assess all substances proposed for use in animals in animals use protocol and review justifications for the use of non-pharmaceutical grade substances proposed by a PI in an IACUC protocol.
- Seek advice from a consultant (e.g. pharmacologist) if none of the IACUC members has the required expertise with a particular substance proposed to be used.

**The Research Integrity office will be responsible for:**

- Administrative support of the IACUC members to facilitate their regulatory function
- Maintaining policy and assure regular review and update as necessary by the IACUC

**The Office of Comparative Medicine (CM) will be responsible for:**

- Assisting the PI and IACUC in reviewing all substances proposed in an Animal Use Protocol and verifying whether it is of pharmaceutical grade
- Offering appropriate alternatives to the PI (if available) for non-pharmaceutical grade substances

VII. Procedures

1. The PI must consider any available pharmaceutical grade compound prior to proposing the use of a non-pharmaceutical grade compound.
2. The use of the non-pharmaceutical grade compound must be described and justified in detail in the animal care and use protocol submitted to the IACUC for review. It cannot be used before IACUC approval has been granted.

VIII. Policy Renewal Date

10/25/2022

IX. References

1. Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals
2. The Guide for the Care and Use of Laboratory Animals, Eighth Edition
3. USDA APHIS Policy #3, "Veterinary Care"

POLICY APPROVAL

*Initiating Authority*

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Name: Daniel C. Flynn, Ph.D., Vice President for Research

Executed signature pages are available in the Initiating Authority Office(s)