



Johns Hopkins University

Animal Care and Use Committee

Use of “Non-Pharmaceutical Grade” Substances in Laboratory Animals

PURPOSE:

This document describes requirements regarding the use of non-pharmaceutical-grade chemicals or compounds in laboratory animals at Johns Hopkins University to remain in compliance with positions held by the Office of Laboratory Animal Welfare (NIH-OLAW), the United States Department of Agriculture -Animal Plant Health Inspection Service (USDA-APHIS) and the *The Guide for the Care and Use of Laboratory Animals* (8th ed., 2011)

BACKGROUND:

Guidance from the National Institutes of Health (NIH) Office of Laboratory Animal Welfare (OLAW) requires that preference be given to “pharmaceutical grade” chemicals and other substances when selecting compounds for use in laboratory animals.¹ An OLAW policy statement² has defined “pharmaceutical grade” compounds as those that have been approved for human or veterinary clinical use by the Food and Drug Administration or those for which a chemical purity standard has been established by the [United States Pharmacopeia-National Formulary](#), or [British Pharmacopeia](#). Just as the delivery of drugs and other substances to laboratory animals must be approved by the ACUC, the choice to use non-pharmaceutical grade compounds must be approved as well. Fortunately, OLAW has indicated that the ACUC may employ “a variety of administrative methods to review and approve” the use of non-pharmaceutical grade substances, including the establishment of “acceptable scientific criteria within the institution, rather than on a case-by-case basis.”² The purpose of this document is to accomplish this objective for JHU and to provide information about the policy to the JHU research community.

I. Drugs used for a clinical purpose in laboratory animals:

Consistent with OLAW requirements, the JHU ACUC expects that drugs that meet the OLAW definition of pharmaceutical grade compounds will be used for sedation/restraint, anesthesia, analgesia, euthanasia, and other clinical purposes in laboratory animals. This policy for use of pharmaceutical grade compounds for “medications” is also consistent with the policies of the

¹ Page 31, *Guide for the Care and Use of Laboratory Animals* (8th edition), published 2011. Adopted as an extension of PHS Policy by OLAW December 1, 2011.

²Policy statement on Non-pharmaceutical grade substances issued 12/1/2011 in response to public comment period ending 5/24/2011; revised 5/29/2012 in response to the public comment period ending 2/3/2012. http://grants.nih.gov/grants/olaw/positionstatement_guide.htm

United States Department of Agriculture's Animal and Plant Health Inspection Service for enforcing the Animal Welfare Act Regulations.³

If a preferred compound is not available as a clinical use formulation, a non-pharmaceutical grade formulation may be used if approved by the ACUC. This applies as well to compounds that typically are available in a pharmaceutical grade preparation but become unavailable for some period of time.

Although OLAW^{1,2} does not consider "cost savings alone" an adequate justification for the use of non-pharmaceutical-grade compounds in animals, it has recognized that from time to time some drugs may be in such short supply, with an accompanying large escalation in cost, that cost may become a relevant variable for approval of a non-pharmaceutical grade compound.⁴

II. Drugs used as research tools or the subject of investigation:

The JHU ACUC recognizes that compounds that fall into the non-pharmaceutical grade category defined above are essential to basic research in many scientific fields, particularly in the bio-medical research that comprises the vast majority of the animal research protocols handled by the ACUC.

The JHU ACUC expects that investigators will consider relevant animal welfare as well as scientific issues in choosing the types and sources of substances to administer to laboratory animals for research purposes. Some of the circumstances that compel use of a non-pharmaceutical grade compound for research include the following:

- The compound is not available in a clinical use formulation.
- The compound is supplied to the investigator through an NIH Drug Supply Program.
- The compound is supplied to the investigator through a JHU-negotiated Material Transfer Agreement with a pharmaceutical or biotechnology firm.
- The investigator has a collaborative research relationship with an academic medicinal chemist to carry out a pharmacological characterization of novel compounds with potential for therapeutic use.

The JHU ACUC also recognizes that when a clinical use formulation has been marketed for a particular compound, it may not be useful for a research purpose due to one or more of the following variables:

- The need to manipulate concentration while holding volume constant. (Adding drug powder or diluting the pharmaceutical grade formulation would obviate its advantage.)
- Lack of the appropriate vehicle control.
- Formulation is inappropriate for the planned route of administration.
- Presence of preservatives or other undesirable components in the formulation.
- The need to hold formulation constant for comparison to previous studies.

As stated above, OLAW does not consider cost savings alone an adequate justification for the use of non-pharmaceutical-grade compounds in animals.^{1,2} They have, however, recognized that from

³ Policy 3, Veterinary Care (www.aphis.usda.gov/animal_welfare/policy.php?policy=3). Applies to species covered by the Animal Welfare Act (generally, mammals other than rats and mice that have been bred for use in research; birds not bred for research also are included).

⁴ Statement by Susan Silk, M.S., Director of the Division of Policy and Education, OLAW: "AAALAC and OLAW Implementation and Recommendations Regarding the New *Guide*. . ." (Scientists Center for Animal Welfare IACUC Training Workshop, Baltimore, MD, April 30, 2012) in relation to the virtual unavailability of pentobarbital sodium except at a cost of \$1000 for 50 ml of 50 mg/ml solution from very limited sources.

time to time some drugs may be in such short supply that cost may become a relevant variable.⁴ Similarly, the JHU ACUC recognizes that due to a continuing need for a particular compound in a research, the pharmaceutical grade formulation may be so expensive as to preclude the investigator from using it on a continuing basis with the research resources available.

Expectations of the JHU ACUC for preparation and use of non-pharmaceutical grade compounds:

The ACUC expects researchers to have the expertise and professional judgment to determine the most appropriate formulation and route of administration for their research. If he/she determines that a non-pharmaceutical grade substance is needed, the ACUC expects that the researcher will obtain the highest quality/purity and will have the expertise, technical information, and laboratory resources for preparing a formulation that is most suitable for the planned route of administration.

Regardless of whether a compound is pharmaceutical or non-pharmaceutical grade, pharmacokinetics may be a variable relevant to choosing one route of administration over another for either clinical or research purposes.

The following variables may be relevant to consider, depending on route of administration, when formulating non-pharmaceutical grade substances for use in laboratory animals: sterility, acid-base balance, pyrogenicity, osmolality, and compatibility of components.^{1,2}

As in any pharmacology study, researchers are expected to anticipate possible side effects and/or adverse reactions that may be relevant to normal functioning of the animal and state these, along with anticipated duration and/or need for treatment, in the protocol.

The JHU ACUC expects that the duration of storage and use of a non-pharmaceutical grade formulation will be compatible with the duration for which the formulation will remain potent, as per technical information available. Methods for preparing and storing formulations must prevent contamination that could adversely affect animal welfare or the interpretation of data. Formulations must be labeled with the name of the compound and the concentration as well as the date of preparation and planned date of disposal.