Purpose:
To prevent contamination, infection or damage to laboratory animals receiving drugs for research purposes, all compounds/substances/chemicals administered parenterally should be pharmaceutical grade. To define compounding medication and outline the proper use of these drugs. This policy provides a definitive position on the use of non-pharmaceutical grade substances in the animal care and use program. The policy is consistent with the NIH/ILAR Guide for the Care and Use of Animals and the Position Statement by the Council on Accreditation, AAALAC International. This policy is also consistent with the OLAW Position Statement on the Guide for the Care and Use of Animals.

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. 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
(3) Specific review and approval by the institutional 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 same and professional judgment, as outlined above, must still apply. It is important to understand that this guideline 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.

**NOTE:** Some readily available commercially produced products are not pharmaceutical grade. For example, here is an excerpt from the Sigma-Aldrich statement of “Terms and Conditions”:

“**Buyer’s use of products** — Seller’s products are intended primarily for laboratory research purposes and, unless otherwise stated on product labels, in Seller’s catalog or in other literature furnished to Buyer, are not to be used for any other purposes, including but not limited to, in vitro diagnostic purposes, in foods, drugs, medical devices or cosmetics for humans or animals or for commercial purposes. Buyer acknowledges that the products have not been tested by Seller for safety and efficacy in food, drug, medical device, cosmetic, commercial or any other use, unless otherwise stated in Seller’s literature furnished to Buyer.”

**Definitions:**

- **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
- **Analytical grade bulk chemical:** ~99% purity; Certificate of Analysis is usually available
- **Non-availability:** Not commercially available from an active US vendor; includes formulations supplied as tablet, capsule, injectable, etc.
- **New 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 nonpharmaceutical grade compound
- **USP/NF:** United States Pharmacopeia/National Formulary
- **BP:** British Pharmacopeia
- **FDA:** Food and Drug Administration; FDA approved compounds are manufactured using USP/NF compounds
- **Compounding:** the combining, mixing, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient.
- **Parenteral:** administered via injection or infusion. Common injection types (IV, subcutaneous (under the skin), and intramuscular (into the muscle)).

**Policy**

Within the Animal Subject Approval Form (ASAF) it is necessary to define whether or not all compounds being administered to research and teaching animals are pharmaceutical grade.
To determine if compounds are pharmaceutical grade, the FDA has a reference that can be used:

- The “Orange Book” is for human FDA approved drugs
  http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

- The “Green Book” is for veterinary FDA approved drugs
  http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/

Pharmaceutical grade compounds occasionally may not be listed in either of these books, but will be labeled with a NDC (National Drug Code), or NADA/ANADA.

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

1. FDA-approved veterinary or human pharmaceutical substances;
2. FDA-approved veterinary or human pharmaceutical substances used to compound a needed dosage form;
3. USP/NF or BP pharmaceutical grade substance used in a needed dosage form (also includes compounded products from any source);
4. Analytical grade bulk chemical used to compound a needed dosage form (requires justification);
5. Other grades and sources of substances (requires justification).

For a majority of common substances used in laboratory animal research, pharmaceutical grade (USP or NF grade) substances are available and should be used. Examples of common substances that are available in USP or NF grades include:

- Saline
- DMSO
- Corn oil
- Tamoxifen
- Tetracycline
- Analgesics (e.g., Buprenorphine)
- Anesthetics (e.g. Ketamine, MS 222)
- Euthanasia agents (e.g. Beuthanasia-D)

**How to determine if your substance is pharmaceutical grade:**

1. Presence of an NDC (National Drug Code) number on the box, bottle, or vial (this number is often in very fine print, and may be difficult to read; however it is a reliable indicator of the substance grade); and
2. Presence of an expiration date; and
3. Presence of a lot number; and
4. Purchased from a USDA licensed vendor or pharmacy, or listed as “pharmaceutical grade” in the vendor catalog
5. Verbiage on box, bottle, or vial stating the product is FDA approved, or the presence of the USP insignia

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

Compounding

The IACUC considers dilutions/mixtures/compounding to be equivalent to pharmaceutical grade as long as all ingredients within the solution/mixture are pharmaceutical grade.

- Sterility and proper storage must be followed during compounding (See preparation methodologies)
- Expiration of pharmaceutical grade mixtures are considered expired three months from the date of preparation.
- All dilutions or mixtures must be labeled minimally with:
  - Active compounds
  - Concentration
  - Preparation date
  - Expiration date

Compound Preparation and Storage Methodologies

- Compounds for injection must be prepared in a sterile manner:
  - Use sterile constituents
  - Mix solutions using sterile technique (hood, open flame, etc.)
  - Pass solution through a syringe filter (0.22um) at the time of preparation into a sterile container (rubber-capped glass bottle)
- Maintain proper storage conditions for the constituents of the solution (proper temperature and light)
- Discard if solution is cloudy, precipitated or discolored
REFERENCES:

- U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care, Policy 3Veterinary Care, April 14, 1997.
- OLAW, PHS Policy on Humane Care and Use of Laboratory Animals, December 1, 2011, Frequently asked questions, F. Animal Use and Management (4)

Policy #29: Reviewed and approved by WSU IACUC: 7.29.15