POLICY ON THE USE OF NON-PHARMACEUTICAL-GRAGE & COMPOUNDED PHARMACEUTICAL GRADE SUBSTANCES

MEMORIAL SLOAN-KETTERING CANCER CENTER
WEILL CORNELL MEDICINE

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POLICY ON THE USE OF NON-PHARMACEUTICAL GRADE & COMPOUNDED PHARMACEUTICAL GRADE SUBSTANCES

The United States Department of Agriculture (USDA) Animal Care Policy # 3 and the Guide for the Care and Use of Laboratory Animals (page 31) require the use of pharmaceutical-grade substances for all animal-related procedures, whenever they are available, even in non-survival procedures. A pharmaceutical-grade substance meets the standards of purity and composition established by the United States Pharmacopeia National Formulary (USP/NF) or the British Pharmacopoeia (BP). Compounds distributed by “chemical vendors” (e.g., Fisher Scientific, Sigma-Aldrich) are not pharmaceutical grade. Dilutions or drug mixtures prepared using only pharmaceutical grade substances are referred to as a compounded pharmaceutical grade substance. Enterally\(^1\) administered substances must be food grade, otherwise it is considered to be non-pharmaceutical grade. The following policy has been established to provide direction as it pertains to the use of non-pharmaceutical grade or compounded pharmaceutical grade substances:

1. Non-pharmaceutical-grade substances can only be used in animals after review and approval by the IACUC. One or more of the following conditions must be met for use by the IACUC:
   a. The research requires use of non-pharmaceutical-grade substances for reasons of scientific necessity;
   b. An acceptable veterinary or human pharmaceutical-grade product is not available;
   c. The USP human or veterinary drug is not available in the appropriate concentration or formulation suitable for route of administration required for the experiment; and/or
   d. A non-pharmaceutical grade substance is required to replicate methods from previous studies.

2. Cost savings is not a suitable justification for the use of non-pharmaceutical-grade substances in animals.

3. The use of non-pharmaceutical-grade substances must be justified and clearly described in the IACUC Protocol. The description should include:
   a. The chemical grade of the substance(s) being used;
   b. The source of the substance;
   c. A description of the appropriateness of the substance(s), its formulation and vehicle;
   d. Method of preparation;
   e. Quality control procedures;
   f. Storage methods and conditions; and,
   g. Maximum duration of use following compounding.

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\(^1\) Enteral administration refers to routes that involve the gastrointestinal tract; including oral, sublingual, and rectal.
4. When reviewing requests for the use of non-pharmaceutical-grade substances, the IACUC will consider the following:

   a. The grade/purity of the substance being proposed. The highest-grade equivalent substance must be used;
   b. Intended route of administration;
   c. Issues such as sterility, pyrogenicity, stability, pharmacokinetics, physiological compatibility, and quality control;
   d. Animal welfare issues related to the use of the agent;
   e. Procedures for monitoring and assessing the potential toxicity or pyrogenicity of the substance;
   f. Scientific Issues related to the use of the agent;
   g. Potential for contamination;
   h. Safety and efficacy of the agent; and,
   i. Potential for the inadvertent introduction of confounding research variables.

5. Dilution, mixing, or transferring substances between containers can affect the sterility and/or stability of the substance. The risk of contamination may affect animal or compromise the validity of the study. Approved non-pharmaceutical grade or compounded pharmaceutical grade substances, must be prepared using the following minimum guidelines:

   a. Medications intended for parenteral administration must be prepared and used under sterile conditions.
      i. They must be sterile diluents such as 0.9% NaCl for injection, bacteriostatic saline, or sterile water for injection. Large irrigation saline or PBS bottles are intended for single use or for diagnostic/laboratory use is not an appropriate source of diluent.
      ii. Compounded solutions must be filtered sterilized using a 0.2-micron filter prior to use.
      iii. New, sterile needles, syringes, and injection vials must be used when preparing and storing the substance.
   b. The pH of the substance must be appropriate for the method of administration. Parenterally administered substances should approximate a physiological pH (7-8) and enterally administered substances should be stable in the stomach.
   c. Whenever possible, drugs should be prepared on the day they will be used.

6. If storage is required, the following steps should be followed:

   a. Prepare the minimal amount necessary to minimize storage time prior to administration;

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2 Parenteral administration refers to routes of administration that do not involve drug absorption via the gastrointestinal tract; including intravenous, intramuscular, retro-orbital, subcutaneous, and transdermal routes.
b. Store according to the manufacturer’s recommendations. Storage Requirements for storage may include: protection from light, refrigeration, and/or use within a specified period of time;

c. Substances intended for parenteral administration require use of a sterile vial with an injection port (available from RARC’s Veterinary Services). If used for multiple doses, the rubber stopper should be swabbed with 70% alcohol before each use. Falcon, Eppendorf, or snap-cap tubes should not be used.

d. Prior to each use, verify that the physical appearance of the substance has not changed since initial preparation. Substances that have changed in color, turbidity, or consistency, or has crystals or sediment should not be used.

e. An appropriate “Beyond-Use Date” (BUD) must be assigned by consulting the scientific literature.
   i. The BUD should never exceed the expiration dates of any of the solution’s components.
   ii. When a BUD for a non-pharmaceutical grade or compounded pharmaceutical grade substance has not been established by the USP, ideally an experimental stability study should be performed to assess the physical, chemical, microbiologic, toxicologic, and stability of these solutions.
   iii. Without specific stability data, when prepared using only pharmaceutical grade substances (e.g., dilutions, drug components of cocktails), SQ, IV, IP formulations should be assigned a BUD as follows:
       1. 30 days at room temperature
       2. 45 days in a refrigerator or freezer
   iv. SQ, IV, IP formulations prepared from non-pharmaceutical grade substances should be assigned a BUD as follows:
       1. 4 days at room temperature
       2. 10 days in a refrigerator
       3. 45 days in a freezer
   v. Without specific stability data, oral, topical/dermal, or mucosal formulations should be assigned a BUD as follows:
       1. Non-preserved aqueous= 14 days
       2. Preserved aqueous= 35 days
       3. Nonaqueous= 90 days
       4. Solid forms= 180 days

f. Label the container appropriately, including:
   i. The full name of each chemical/drug and diluent in the container;
   ii. Final concentration of each drug in mg/ml;
   iii. The date the substance was prepared or diluted;
   iv. The manufacturer provided expiration dates of each added chemical/drug, if no date is provided, use a date of 5 years after opening\(^3\); and,
   The “Use by” date.

\(^3\) [https://www.triumvirate.com/blog/making-sense-of-the-expiration-or-retest-date-on-your-labs-chemical-bottles](https://www.triumvirate.com/blog/making-sense-of-the-expiration-or-retest-date-on-your-labs-chemical-bottles)