IACUC Policy on the Use of Non-Pharmaceutical Grade Substances and Expired Material

In accordance with USDA[1] and OLAW[2,3] policy, the University of South Carolina requires that pharmaceutical grade substances (e.g., fluids, compounds, medications, drugs, vehicles, and diluents) be used in all cases in which they are available. This policy applies to all vertebrate species and includes survival as well as non-survival procedures. The IACUC may approve the use of non-pharmaceutical grade substances under certain circumstances, such as those cases in which pharmaceutical grade alternatives are not available, or not available in the required formulation or concentration, or do not exist in a form compatible with the intended route of administration. Approval in these cases is contingent on institutional review by the IACUC

Definitions

A pharmaceutical grade compound 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[4] (e.g. the U.S. Pharmacopeia (USP), British Pharmacopeia (BP), National Formulary (NF), European Pharmacopeia (EP), 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. *Pharmaceutical grade drugs are formulated to a standard compatible with the legal and ethical treatment of human or veterinary patients in a health care or practice setting by a pharmaceutical company or qualified compounding pharmacist.*

A non-pharmaceutical grade compound is any compound that has not been formulated for the production of medicine. Agents obtained from chemical supply companies and or prepared in a research laboratory are of reagent and not pharmaceutical grade.

General Guidelines for Selecting Compounds

When selecting compounds, the following options are listed in order of preference: Any compound that is not FDA approved will require approval by the IACUC.

1. FDA approved veterinary or human pharmaceutical compounds.

2. A drug preparation prepared by a licensed compounding pharmacist using FDA approved veterinary or human pharmaceutical compounds and/or USP/NF or BP pharmaceutical grade compounds to prepare a final product in a needed dosage form.

3. A final compound prepared in the laboratory using FDA approved veterinary or human pharmaceutical compounds and/or USP/NF or BP pharmaceutical grade compounds to prepare a needed dosage form.

4. A final compound prepared in the laboratory using any analytical grade bulk chemicals to prepare a needed dosage form.

5. A final compound prepared in the laboratory using any other grades and sources of compounds to prepare a needed dosage form.

Requirements for the Use of Non-Pharmaceutical Grade Substances

Both USDA and OLAW regulations indicate that "the IACUC should develop a consistent evaluation process that includes but is not limited to the scientific justification and the availability of an acceptable veterinary or human pharmaceutical-grade product. Cost savings alone is not sufficient justification for using a non-pharmaceutical-grade substance in regulated species. A history of the use of a non-pharmaceutical grade substance alone is not a sufficient justification for continued use. In almost all cases, analgesics and anesthetics must be pharmaceutical grade."

To secure approval for the use of non-pharmaceutical grade substances, the PI must (1) provide sound scientific justification for the use of the compound, (2) verify that the compound is not available as a pharmaceutical grade product in the required formulation or concentration (if available in higher concentrations than needed, identification of the diluent is necessary and dilution with a pharmaceutical grade diluent is generally required), and (3) justify use of the NPG product as an appropriate alternative.

Required information in the justification for a non-pharmaceutical grade substance includes a description of the means to assure purity, sterility, and stability. Parenterally (IV, SC, IM, IP) administered compounds must be **sterile** and **pyrogen-free**. Sterility can be accomplished by steam autoclaving, dry heat sterilization, irradiation, sterile filtration, etc. dependent upon the compound and the diluent used. Pyrogens can be avoided by using purified and characterized compounds and diluents in preparation of the final drug. Unlike osmolality and pH, sterility is critical for parenteral administered drugs regardless of the route of administration or volume of drug being administered.

Diluents and solvents used for reconstitution should be pharmaceutical grade when available. Compounds reconstituted for multi-use must be labeled identifying the compound, concentration or activity, the date of preparation, the initials of the person who prepared the solution/suspension and the expiration date. Reconstituted compounds should be discarded before degradation occurs. If degradation is unknown, fresh compound must be prepared each time. All manufacturer guidelines must be followed.

In addition, information needed for review includes the site and route of administration, and potential side effects and adverse reactions. Other variables that investigators should consider and may wish to provide include information regarding the grade, acid-base balance, pyrogenicity, osmolality, compatibility of components, and pharmacokinetics of the NPG compound. Investigators may refer to sources of information such as QC data sheets from the manufacturer, references to previous publications using the substance, and/or documentation of independent testing for purity or sterility. Further guidelines are provided below.

Other Considerations for Non-pharmaceutical Grade Substances

The IACUC will generally not require specific details on drug osmolality, osmolarity, or pH unless it has specific concerns about the volumes and/or compounds being proposed.

> Osmolality: Normal plasma has an osmolality in the range of 285-295 mOsm/kg (osmolarity range of 300-310 mOsm/L) and intravenously administered compounds should generally be formulated to a range matching this osmolality as closely as possible. Agents with an osmolality greater than 600 mOsm/kg cause red blood cell crenation upon intravenous injection while agents less than 150 mOsm/kg will cause hemolysis, both of which are associated with pain and physiologic disturbances. Solutions with an osmolality less than 450 mOsm/kg are generally well

tolerated by intravenous infusion. Agents with widely non-physiologic osmolality administered via other routes (IM, SC, IP) may result in localized tissue damage and associated pain upon injection. As the volume of injected compound increases the potential for tissue damage and pain due to non-physiologic osmolality also increases dramatically. If an investigator has concerns regarding the osmolality of a solution they should measure osmolality on an osmometer. Osmolarity/osmolality calculators are available on the internet to assist in calculating predicted drug osmolality/osmolarity for solutions of mixed compounds (http://www.rxkinetics.com/iv_osmolarity.html).

pH: Plasma pH is tightly regulated normally between 7.35 and 7.45. The administration of compounds with widely variant pH values may impact the overall normal physiologic acid-base balance and result in pain and distress upon injection. Acidic (<4) and alkaline (>11) solutions should be avoided and if required, should be administered in small overall volumes. Solutions compounded within a pH range of 6.5 to 8.0 are generally well tolerated in continuous intravenous infusions while solutions in the pH range of 5-9 can be tolerated for a shorter duration.

Expired Materials

The use of expired medical materials such as drugs, fluids, or sutures is not considered to be acceptable veterinary practice and does not constitute adequate veterinary care. All expired medical materials must either be disposed of or segregated into an appropriately labeled, physically separate location from non-expired medical materials.

References

Division of Compliance Policy Guidance for FDA Staff and Industry, Compliance Policy Guides Manual Sec. 608.400 Compounding of Drugs for Use in Animals. Division of Compliance Policy (HFC-230, Food and Drug Administration).

Institute of Laboratory Animal Resources (U.S.). 2011. *Guide for the Care and Use of Laboratory Animals*. Washington, D.C.: National Academy Press.

United States., United States. Animal and Plant Health Inspection Service. 2017. *Animal Welfare Act and animal welfare regulations*. Washington, D.C.: U.S. Dept. of Agriculture, Animal and Plant Health Inspection Service.