IACUC POLICIES, PROCEDURES and GUIDELINES

Use of Non-Pharmaceutical Grade Compounds

119.1 PURPOSE

This document details IACUC policies and expectations regarding the use of non-pharmaceutical grade compounds in laboratory animals used in research, teaching, and testing at the University of Kentucky.

119.2 BACKGROUND

The Guide for the Care and Use of Laboratory Animals (2), the Animal Welfare Regulations (3), the Office of Laboratory Animal Welfare (OLAW) of the Public Health Service (http://www.grants.nih.gov/grants/olaw/faqs.htm#f4) and Animal Care of the United States Department of Agriculture (http://www.aphis.usda.gov/animal_welfare/policy.php?policy=3) have stated that pharmaceutical-grade chemicals and other substances, when available, must be used to avoid toxicity or side effects that may threaten the health and welfare of vertebrate animals and/or interfere with the interpretation of research results. Non-pharmaceutical grade chemical compounds should only be used after specific review and approval by the IACUC for reasons such as scientific necessity or non-availability of an acceptable veterinary or human pharmaceutical-grade product. Cost savings is not a justification for using non-pharmaceutical-grade compounds.

Additionally, the Food and Drug Administration (1) specifically prohibits the extra-label use of any drug or the use of compounded drugs in food producing animals without a specific prescription written by the licensed veterinarian after the establishment of a valid veterinary-client relationship (21 CFR §530 Subpart C).

119.3 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 non-pharmaceutical 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

119.4 RESPONSIBILITIES

Investigator:

Investigators are responsible for ensuring that pharmaceutical grade compounds are used whenever they are available. The use of non-pharmaceutical grade anesthetics, analgesics, antibiotics, or euthanasia drugs is especially problematic since the intent of these drugs is to treat potential pain and distress or prevent infection. When pharmaceutical grade compounds are not available the investigator must provide specific details regarding the non-pharmaceutical compound use being proposed and scientific justification for such use. If applicable, as in the case of anesthetics, analgesics, euthanasia compounds, etc., the use of alternative strategies using available pharmaceutical compounds must be addressed.

The investigator must also provide sufficient information to the IACUC to permit the IACUC to assess the potential of the non-pharmaceutical grade drug to harm animal health or well-being. This should include specifics regarding the toxicity of the drug components if known, and details regarding the drug preparation where the drug is not a pharmaceutical grade drug and is not compounded by a licensed pharmacist. This should include information regarding the actual drugs used for the preparation (sterility, chemical grade, drug contaminants, etc.), approximate drug pH and osmolality, drug stability and storage, final product sterility, and any quality control procedures used to test the final product.

IACUC:

The IACUC is responsible for evaluating the potential adverse consequences of such agents when used for research. The IACUC should consider the as applicable and relevant to the specific circumstance: 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, storage, and quality control.
119.5 SELECTING DRUGS, CHEMICAL, AND COMPOUNDS FOR USE IN ANIMALS

119.5.1 General Guidelines for Compounding Drugs

Osmolality and pH: Control of drug osmolality and pH is most critical when drugs are administered via the intravenous route and when large volumes are being administered. In cases where small volumes are administered the effect of osmolality and pH is relatively minor except in extreme cases. The IACUC will generally not require details on drug osmolality, osmolarity, or pH except in protocols where large volumes of non-pharmaceutical drugs or certain non-pharmaceutical drug formulations are used.

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. Osmolarity/osmolality calculators are available on the internet to assist in calculating predicted drug osmolality/osmolarity (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.

Sterility and Pyrogenicity: Parenteral (IV, SC, IM, IP) administered compounds should 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.
119.5.2 General Guidelines for Selecting Drugs

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

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. In these cases the licensed compounding pharmacist will ensure that the drug meets the appropriate criteria for its intended route of administration;

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. Specific details as to method of preparation, sterility, pH, osmolality, specific quality control procedures, stability, storage conditions, and expiration date must be detailed to allow IACUC review and evaluation of potential adverse effects;

4. A final compound prepared in the laboratory using any analytical grade bulk chemicals to prepare a needed dosage form. Specific details as to purity of the bulk chemical, method of preparation, sterility, pH, osmolality, specific quality control procedures, stability, storage conditions, and expiration date must be detailed to allow IACUC review and evaluation of potential adverse effects;

5. A final compound prepared in the laboratory using any other grades and sources of compounds to prepare a needed dosage form. Specific details as to purity of the bulk chemical (if known), potential contaminants (if known), method of preparation, sterility, pH, osmolality, specific quality control procedures, stability, storage conditions, and expiration date must be detailed to allow IACUC review and evaluation of potential adverse effects.
REFERENCES

