

Proper Preparation, Dilution, Usage and Storage of Drugs, Medical Materials and Controlled Substances

Re-Approved by UCAR 9-21-22

The Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals require that research animals be provided with adequate veterinary care 1, 11. The administration of expired medical materials, nonpharmaceutical grade chemical compounds and/or their improper storage is considered inadequate veterinary care. In addition, these management problems constitute a violation of the policies of the University of Rochester, University's Assurance with the Public Health Service (PHS) and United States Department of Agriculture (USDA) regulations.

Definitions

Aseptic technique requirements: 1) a new sterile needle is used every time, 2) a new sterile syringe is used at least daily, 3) if the inside of the syringe is exposed to animal fluids then it should be discarded, and 4) the collection port is wiped before each draw with 70% alcohol. Any break in aseptic technique described above and in the referenced article may result in contamination of the fluids with bacteria and endotoxins.

Medical Material: Any article intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans or animals and articles intended to affect the structure or any function of the body of humans or animals.⁴

Drugs Administered for Therapeutic Purposes

Medical materials intended for administration to animals such as drugs, fluids and sutures must be used within their shelf life. Anesthesia, analgesia, emergency drugs, and euthanasia drugs must be pharmaceutical grade and must be used before their expiration dates.⁷ For acute terminal procedures, where an animal is put under anesthesia, the research carried out (surgery or testing of a compound) and the animal is euthanized without ever waking up, medical materials may be used beyond their "to be used by" date if such materials' use does not adversely affect the animal's wellbeing or compromise the validity of the scientific study. When investigators wish to use expired materials for acute, terminal procedures excluding anesthetics, analgesics, emergency drugs and euthanasia drugs, the medical materials to be used must be described in the protocol. Such materials must be prominently labeled "For terminal procedures only."

Medical Material inventories should be routinely monitored for expiration and any outdated materials must be immediately discarded. In special circumstances in which drugs cannot be disposed of immediately or for expired materials that are approved in the protocol to be used for acute, nonrecovery procedures, they must be labeled "expired" and physically segregated from other materials until proper disposition is possible. All containers must be labeled with medical "materials" name and expiration date of each medical material (e.g. ketamine exp. 01/10, Xylazine exp. 01/10 & saline exp. 01/10).

Controlled Substances

Controlled substances (CS) such as anesthetics, analgesics and euthanasia agents may be ordered from SMD Pharmacy using the URM 312 Requisition form. The SMD Pharmacy Policy 10 G requires investigator to:

- Store CS in wall mounted, double lock narcotic cabinet,

- Secure the keys to the narcotic cabinet,
- Document after each use of the CS
- Uniquely identify each bottle of CS which matches the CS log sheet,
- Maintain current inventory after each use,
- and store only CS in the narcotic lockbox.

If barbiturate agents (i.e. pentobarbital) are in short supply, pharmacy may recommend an alternative euthanasia solution (SleepAway®, Euthasol®, Beuthanasia®, etc) that can be ordered. Use of this alternative euthanasia agent will not require a modification to your protocol.

- Important note: Euthanasia agents containing pentobarbital MAY NOT be substituted for pentobarbital or other agents for recovery procedures.

If an investigator orders controlled substances using his/her own DEA number for use in live animal research, he or she is responsible for secure storage, accurate documentation, proper disposal (surrender) and use of compounds that are not expired.¹²

Substances Administered for Experimental Purposes

Non-pharmaceutical-grade chemical compounds used for experimental purposes must meet the requirements described in UCAR's Non Pharmaceutical Grade Substance Policy.^{6,8}

Preparation and Handling of Medical Materials

Medical Materials administered to animals must be handled and stored to maintain sterility. This is accomplished by:

- Appropriate closed sterile containers (e.g. injection vials, red-topped blood tubes)
- Mixing the smallest amount of agent suspension/dilution/mixture needed to minimize storage time
- Using aseptic technique when adding or withdrawing solutions
- Using clean, sterile container for each preparation (do not reuse)

Drugs and fluids must be stored in ways that will not affect their efficacy upon administration to animals. Improper storage of such materials includes the following: 1) storage in a dirty environment, e.g. permanent placement of a hypodermic needle in the top of a multi-dose vial 2) storage in an unsuitable environment, e.g. maintaining drugs intended for refrigeration at room temperature or not storing light sensitive drugs in amber or covered bottles and 3) storage of drugs in unlabeled containers or syringes.

Dilutions Mixtures and stock solutions stored in sterile secondary containers

- In-house made anesthetic cocktails and diluted medications must use sterile, pharmaceutical grade compounds, must be combined using sterile technique, and be stored in a sterile vial in a cool place and away from light.
- Vials of compounded drugs must be labeled with the final concentration of each component, preparation and expiration dates, and the initials of the person preparing the compound.
- Sterile dilutions or mixtures of medical materials may result in a shorter effective expiration date than the expiration date of the individual components, due to risk of contamination, dilution of preservatives, and interactions between the compounds.
- Containers of parenteral fluids (e.g. lactated ringers, saline, phosphate buffered saline) or fluids used as diluents (sterile saline, etc.) which are injected into animals should have

the date of first use written on them. Fluids that contain sugar (e.g. glucose, dextrose) should be discarded 12 hours after they are opened because of their ability to support microbial life if contaminated. All other fluids where **aseptic technique*** is used must be discarded 30 days after their first use.²

- The expiration date (use-by date) for dilutions; medications from stock vials stored in secondary containers (i.e. sterile vials, sterile tubes or bottles) and cocktails of anesthetics (e.g., ketamine + xylazine) and other drugs will be 30 days from the date of compounding or the earliest expiration date of any single compound used, whichever is first.²

- Mixtures may be given extended expiration dates if scientifically justified (e.g. if there are published studies of stability or the PI provides evidence that the mixture is stable, sterile and effective for longer than 30 days).³

- For tribromoethanol (TBE, Avertin), please refer to the TBE policy.

Laboratory Inspections

Throughout the year, the University of Rochester is subject to unannounced inspections by two important governing agencies. USDA and New York State inspectors visit animal housing areas, procedure rooms, surgical facilities and laboratories where animals are taken for research. If improperly prepared or stored drugs, or expired medical materials are identified, the institution may be cited for veterinary deficiencies.

It is the Principal Investigator's responsibility to establish laboratory procedures that ensure that medical materials intended for administration in animals are used appropriately. If you have any questions regarding this policy, please contact the UCAR office at X5-1693.

References:

1. Assessment of stability of ketamine-xylazine preparations with or without acepromazine using high performance liquid chromatography-mass spectrometry. CJVR 80 (2016): 86-89.
2. Assessment of Sterility in Fluid Bags maintained for Chronic Use. JAALAS 50(5) (2011):708-712.
3. Beyond-use Dating of Extemporaneously Compounded Ketamine, Acepromazine, and Xylazine: Safety, Stability, and Efficacy over Time. JAALAS 48 (6) (2009): 718-26.
4. Federal Food, Drug and Cosmetic Act, 21 USC § 321 (2013).
5. National Research council. *Guide for the care and use of laboratory animals*. National Academies Press, 2010.
6. OLAW FAQ F.4 accessed June 23, 2017 "May investigators use non-pharmaceuticals, biologics, and supplies in animals?"
7. OLAW FAQ F.5 Accessed June 23, 2017 "May investigators use expired pharmaceuticals, biologics and supplies in animals?"
8. UCAR Non-Pharmaceutical Grade Substance Policy

9. URMIC, Department of Pharmacy Policy and Procedures (Inpatient Pharmacy) – Controlled Substance in Animal Research Labs (10G).
10. USDA APHIS Animal Care Resource Guide Policies, AC 3.1
11. USDA APHIS Animal Welfare Regulations, 9 CFR § 2.33 (2008).
12. U.S. Department of Justice, Drug Enforcement Administration, Diversion Control Division