THE USE OF PHARMACEUTICAL AND NON-PHARMACEUTICAL GRADE COMPOUNDS IN ANIMALS AND LABELING EXPECTATIONS

Background

Federal regulations require Investigators to use pharmaceutical-grade compounds for **injection** in animals, even in acute procedures including euthanasia. This includes, but is not limited to, medications/drugs, vehicles, and diluents. Pharmaceutical-grade compounds meet established standards of purity and composition helping ensure animal health and experimental results.

It is recognized that many experimental compounds used in research are not available as pharmaceutical grade, or that pharmaceutical grade compounds may need to be diluted or combined for use in laboratory animal research. The use of chemical grade compounds, compounded drugs, or dilution of drugs can introduce unexpected or even toxic effects, and should be avoided whenever possible. When chemical grade reagents or compounding is necessary, this must be done using aseptic technique and the final product must be labeled and stored appropriately.

The use of non- pharmaceutical-grade compounds in laboratory animals must be listed in the animal use protocol and approved by the IACUC.

Definitions

1. *Pharmaceutical-grade compounds* are any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices, which is approved, conditionally approved, or indexed by the FDA or for which a chemical purity standard has been written or established by a recognized compendia, such as the US Pharmacopeia-National Formulary and the British Pharmacopeia. USP labeling does not equate to pharmaceutical grade.

2. *Non-Pharmaceutical-grade (NPG) compounds* are chemicals or compounds that do not meet the criteria noted above in respect to pharmaceutical grade compounds. This would include pure chemicals obtained from any chemical supplier that require reconstitution. PBS is also considered non-pharmaceutical as it is not intended for parenteral injection.

3. *The United States Pharmacopeia National Formulary (USP-NF)* provides FDA-enforceable quality standards for drugs, dietary supplements, and excipients as well as procedures for tests, assays and analytical methods. *Parenteral articles* meet Pharmacopeia requirements for sterility, pyrogens, particulate matter, and other contaminants, and, where appropriate, contain inhibitors of the growth of microorganisms.

4. *An Injection* is a preparation intended for administration through the skin or directly into a blood vessel, organ, tissue, or lesion.

5. *Compounding* is a practice in which a person combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient(s).

Requirements

All agents used in animals **must** be listed in the IACUC protocol. If compounding of drugs to be injected in animals is necessary, investigators must ensure:

1. **Aseptic preparation** (compounding) of the drug including preparation and storage in sterile vials and filtration or autoclaving of compounded drug if original components are not sterile. Injectable drugs should never be used if they contain particulate matter, precipitates, turbidity, or discoloration.

2. **Appropriate storage** of the compounded drug to include the use of a secondary container and methods which maintain sterility yet allows repeat draws e.g. use of a sterile injection vial with a rubber stopper. Alternatively, for single use purposes, a sterile microfuge tube can be used.

3. **Appropriate labeling** of containers for storage of compounded drugs to include**:**
    A. Name of the compound(s) and diluent (when applicable)
    B. Final concentration (usually mg/ml)
    C. Date of Expiration
        i. Mixtures/Dilutions: The earliest expiration date listed on the stock bottles of agents used
        ii. Experimental (NPG) compounds: The expiration date should be based on performance evaluation of the agent(s) for efficacy as well as consideration of the frequency of use/method of storage.

Note: It is highly recommended when using compounded drugs that a lab-specific SOP be created to establish a proper preparation procedure and expiration for the compounded drug. The length of time a compounded drug can be used should be based on use frequency and performance. Compounded drugs may result in decreased "shelf-life" compared to the stock drug(s). Furthermore, the potential for bacterial contamination is increased when compounding drugs or when drawing from multi-use vials.

4. **IACUC approval** for the use o**f Non pharmaceutical grade compounds is** based on:
    A. Scientific necessity
    B. Non-availability of an acceptable veterinary or human pharmaceutical-grade compound or formulation
    C. Appropriate process for aseptic preparation of compounded drugs for injection in animals
    D. Cost savings is not a justification for using non-pharmaceutical-grade compounds, although OLAW and USDA have made exceptions in cases of limited access resulting in exorbitant costs.

References

1. USDA APHIS Animal Care, Policy 3, March 14, 2014.
2. FAQs about the PHS Policy on humane care and use of laboratory animals. Wolff A, et al. Lab Animal (NY). 2003 Oct; 32(9):33-6.
3. Animal Research Advisory Committee Guidelines _Guidelines for the Use of Non – Pharmaceutical Grade Compounds in Laboratory Animals http://oacu.od.nih.gov/ARAC/index.htm, NIH, OLAW
4. OLAW: Educational Resources: Use of Non- Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals http://grants.nih.gov/grants/olaw/educational_resources/webinar_06042015.htm
5. The United State Pharmopeia National Formulary http://library.ohio-state.edu/record=b5907458~S7
6. The Orange Book is the reference for FDA-approved human drugs. http://www.accessdata.fda.gov/scripts/cder/ob/eclink.cfm
7. The Green Book is the reference for FDA-approved veterinary drugs. http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/

Institutional Approved SOP for Use of Non-Pharmaceutical-Grade Compounds: Tribromoethanol (Avertin)

Background

Tribromoethanol (TBE), commonly referred to by the brand name Avertin, has been used as an anesthetic agent for mice. There have been a number of published reports of adverse effects subsequent to the use of TBE as an intraperitoneal anesthetic in mice usually as a result of improper mixing and storage. Regulatory agencies have subsequently recommended that the use of TBE be discontinued as an anesthetic in mice when possible. Avertin is only available as a non-pharmaceutical grade compound.

Use

TBE is an anesthetic that provides rapid induction and recovery for single use, short duration (approximately 15-20 minutes) surgical procedures in rodents. Improper preparation, storage, or use of Tribromoethanol can result in severe side effects or ineffective anesthesia. Specifically, TBE degrades in the presence of heat and light, producing toxic byproducts that are potent gastrointestinal irritants. The scientific literature indicates that TBE is associated with significant side effects including peritonitis, ileus, and death, particularly when repeated doses are administered. Although TBE is not available as a pharmaceutical grade compound, alternative options for rodent anesthesia include both pharmaceutical grade injectable and inhalation options. ULAR veterinary staff is available to discuss alternatives to the use of TBE.

The body of scientific literature on this compound, as well as the regulatory requirement to use pharmaceutical-grade drugs in animals, presents a compelling case for discontinuing the use of TBE. The IACUC will review the continued use of TBE at the time of three-year renewal on a case-by-case basis; researchers will be required to provide justification for the use of this agent for survival surgery.

Storage and expiration period

TBE must be stored at 2-8°C in light-protected containers. When stored at this temperature, the solution may be used for up to two weeks. Frozen TBE solution can be stored at -80°C for up to 6 months.

The animal use protocol can reference this SOP or alternatively provide details regarding the preparation of the working solution and proper storage of the stock solution in the animal use protocol.

References

1. Papaioannou, VE and Gox, JG. Efficacy of Tribromoethanol Anesthesia in Mice. *Laboratory Animal Science*, 1993. April, 43(2): 189-192.
2. Zeller, WM; Burki, G; and Panoussis, B. Adverse Effects of Tribromoethanol as Used in the Production of Transgenic Mice. *Laboratory Animal Science*, 1998. October, 32(4): 407-413.
3. Kohn, DF; Wixson, SK; White, WJ; and Benson, GJ. *Anesthesia and Analgesia in Laboratory Animals*, 1997.
4. Lieggi, C.C., et al., Efficacy and safety of stored and newly prepared tribromoethanol in ICR mice. Contemp Top Lab Anim Sci, 2005. 44(1): 17-22.
5. PHS Policy on the Human Care and Use of Laboratory Animals, Frequently Asked Questions
6. Lieggi, C.C., et al., An evaluation of preparation methods and storage conditions of tribromoethanol. Contemp Top Lab Anim Sci, 2005. 44(1): 11-6.
7. Meyer, R.E. and R.E. Fish, A review of tribromoethanol anesthesia for production of genetically engineered mice and rats. Lab Anim (NY), 2005. 34(10): 47-52.
8. Zeller, W., et al., Adverse effects of tribromoethanol as used in the production of transgenic mice. Lab Anim, 1998. 32(4): p 407-13.
9. Koizumi, T., H. Maeda, and K. Hioki, Sleep-time variation for ethanol and the hypnotic drugs tribromoethanol, urethane, pentobarbital, and propofol within outbred ICR mice. Exp Anim, 2002. 51(2): p119-24. National Human Genome Research Institute Guideline 03.2, http://www.theodora.com/rodent_laboratory/guideline_03_2.html

Institutional Approved SOP for Use of Non-Pharmaceutical-Grade Compounds: Saturated Potassium Chloride (KCl)

Background

The American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals states that intravenous or intracardiac injection of a solution of supersaturated potassium chloride into an animal under general anesthesia is an acceptable method to enact a quick and humane death consistent with adequate veterinary practices. This method of euthanasia is preferable when euthanizing livestock or wildlife species to reduce the risk of toxicosis for predators or scavengers in situations where carcasses of euthanized animals may be consumed. Saturated KCl is only available as a non-pharmaceutical grade compound.

Use

The potassium ion is cardiotoxic, and rapid intravenous or intracardiac administration of 1 to 2 mmol/kg of body weight will cause cardiac arrest. Saturated potassium chloride has been commonly used to euthanize large animals (rabbits, dogs, cats, sheep, pigs, etc.) under general anesthesia as approved in the AVMA Guidelines for the Euthanasia of Animals. Saturated potassium chloride is not available in a pharmaceutical grade form. Scientific justification for the use of this euthanasia method is to accomplish a quick and humane death during a non-survival procedure in an animal that is under general anesthesia and this agent does not contaminate the animal carcass per environmental landfill requirements.

References

1. AVMA [American Veterinary Medical Association]. 2020. Guidelines for the Euthanasia of Animals. Schamburg, IL: AVMA.
2. U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care, Policy 3- Veterinary Care, April 14, 1997.
3. Barbiturates. In: Ciganovich E, ed. *Field manual of wildlife diseases*. US Department of the Interior/US Geological Survey, Biological Resources Division, Information and Technical Report 199-2001.
4. Lumb W. Euthanasia by noninhalent pharmacologic agents. *J Am Vet Med Association*. 1974; 165: 851-852.

History of Revisions

045-00 - new policy approved 12/14/12
045-01 – revised made and approved 10/18/13
045-02 – the title was revised and clarifications were described for definitions, preparation, storage, and labeling expectations, approved 07/15/16
045-03 – the definition on pharmaceutical-grade compounds was updated to clarify that USP labeling does not equate to pharmaceutical grade, approved 12/21/18.
045-04 – definitions were revised and requirements reorganized; approved 12/17/21