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IACUC GUIDELINE:	ADMINISTRATION OF EXPERIMENTAL SUBTANCES TO ANIMALS, INCLUDING NON-PHARMACEUTICAL-GRADE OR CONTROLLED SUBSTANCES
DATE IMPLEMENTED:	December 11, 2009
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This IACUC guideline was created to provide guidance to investigators and to set clear expectations on the administration of experimental substances to animals, including the conditional use of non-pharmaceutical-grade substances. This document also clarifies the record keeping, storage, and labeling procedures for all laboratories administering non-pharmaceutical-grade or controlled substances to animals. The Operational Guideline has been appended to the end of this IACUC guideline.

All experimental substances administered to animals must be listed in the animal protocol (i.e., table 12 of the protocol application form) for IACUC review. Similarly, the addition of a new (i.e., not in the original protocol) experimental substance to an approved protocol requires IACUC review, as does any significant change[1] to a protocol. However, in order to provide for a timely review while ensuring animal welfare, this proposed significant change may be handled administratively in consultation with the Attending Veterinarian (AV), if all of the following conditions apply:

1. The administration of the new experimental substance doesn't result in greater pain or distress to the animal.

2. The addition of a new experimental substance fits within the study objectives of the protocol, and doesn't involve the addition of a new experimental procedure.

3. The experimental substance being added to the protocol is administered to animals according to a dose and route of administration that conforms to an established veterinary drug formulary and practice, and/or FDA Guidance on inter-species dose translation[2] or appropriate reference in the scientific literature.

4. The formulation, storage and labeling of the experimental substance, if it's not a pharmaceutical-grade substance as defined below, will conform to the procedures for using non-pharmaceutical-grade substances that are also described below.

Relevant Federal Regulations and Guidance:

The Office of Laboratory Animal Welfare (OLAW)[3-5], Office of Extramural Research NIH, and Animal and Plant Health Inspection Service (APHIS)[6], United States Department of Agriculture (USDA) have clarified the following requirements regarding the use of non-pharmaceutical-grade substances and expired drugs or medical materials:

1. Pharmaceutical-grade 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.

2. A pharmaceutical-grade substance is any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices (GMP) which is approved, conditionally approved, or indexed by the Food and Drug Administration (FDA) or for which a chemical purity standard has been written or established by a recognized compendia (e.g., United States Pharmacopeia-National Formulary (USP-NF), British Pharmacopeia (BP)).

3. The IACUC is responsible for evaluating the potential adverse consequences of non-pharmaceutical-grade substances when used for research.

4. The use of expired pharmaceuticals, biologics, and supplies is not consistent with acceptable veterinary practice or adequate veterinary care. Euthanasia, anesthesia and analgesia agents should not be used beyond their expiration date, even if a procedure is terminal. Other expired materials should not be used unless the manufacturer verifies efficacy beyond the expiration date, or the investigator is able to document to the satisfaction of the IACUC that such use would not negatively impact animal welfare or compromise the validity of the study. The veterinarian and IACUC must maintain control over the use of expired medical materials in order to meet their responsibilities to avoid or minimize discomfort, pain or distress to animals.

IACUC Expectations:

In order to protect animal welfare, due consideration must be given to the preparation (grade, purity, sterility, biocompatiblity, and stability) and storage of any experimental substance that is administered to animals. Approval for the use of non-pharmaceutical-grade substances will be made on a case-by-case basis by weighing the potential adverse consequences to the animal against scientific criteria for the use of these substances. "Cost savings alone are not an adequate justification for the use of non-pharmaceutical-grade substances in animals. However, unavailability or shortages of pharmaceutical-grade substances may lead to cost increases and the IACUC may determine that this justifies the use of the non-pharmaceutical-grade substitution."[3, 4]

The IACUC has established an Operational Guideline[7] for preparing, storing and labeling drugs and experimental substances, which is briefly summarized below.

- Use chemicals of the highest grade and purity.

- Use only sterile chemicals/compounds/drug solutions intended for parenteral (i.e. IV, IP, IM, or SC) administration. Use of a syringe-top filter (0.2 µm) is recommended for solutions that cannot be sterilized by other methods.

- Use only sterile and biocompatible (physiological pH and osmolality) solutions to dissolve or dilute the experimental substances.

- Use appropriate precautions to prevent microbial contamination when preparing non-pharmaceutical-grade substances or when compounding[7] pharmaceutical-grade drugs. Manipulate all sterile products aseptically, including donning appropriate PPE and/or working in a biological safety cabinet or laminar flow hood (clean bench).

- If information is not available on the chemical stability of the specific experimental substance, then storage conditions will follow standards set forth by the USP Compounding Compendium (<797> Pharmaceutical Compounding – Sterile Preparations)[8] and/or will be based on drug stability and sterility testing results.

- All experimental substances should be labeled with the drug/substance name, a preparation date and a use-by or beyond-use date (i.e., the date on which the product must be discarded).

The acquisition, storage, and research use of controlled substances (e.g. ketamine, pentobarbital, or cocaine) must conform to DEA regulations and the Best Practices Guide from the UC Office of the President (BUS 50), and in the future the UCSB Controlled Substance Program administered by EH&S. At a minimum, all controlled substances should be securely stored; each drug vial or container should be uniquely identified and clearly labeled with the name, concentration, and expiration date of the drug; and the research use of controlled substances should always be properly documented to enable audit tracking by UCSB officials (i.e. IACUC or EH&S) or federal agents (i.e. DEA or USDA). Further, it is recommended that the following information should be documented: the name of the drug, date of use, brief description of use (e.g. anesthesia, or euthanasia), species and number of animals dosed, amount of drug used, calculated balance of drug remaining in the vial, and the initials of the individual dispensing and administering the drug.

Resources for Locating Pharmaceutical-Grade Substances for In-Vivo Use

Online

- DailyMed

- FDA Orange Book, which list approved human drug products.

- Animal Drugs @ FDA

Publications

Pharmaceuticals for use in humans and animals: *Physician's Desk Reference* (which is also accessible electronically) and the *Veterinary Pharmaceuticals and Biologicals*, and a search on a web search engine may provide a monograph for any drug labeled for human or animal use. It is suggested that both these resources be considered. Drug monographs will also list brand names with formulations and concentrations that are offered.

Reference:

1. Guidance on Significant Changes to Animal Activities. National Institutes of Health. NOT-OD-14-063.

2. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Pharmacology and Toxicology. July 2005.

3. OLAW Webinar: "Regulatory Considerations for Using Pharmaceutical Products in Research Involving Laboratory Animals - June 4, 2015"

4. OLAW FAQ: "May investigators use non-pharmaceutical-grade substances in animals?"

5. OLAW FAQ: "May investigators use expired pharmaceuticals, biologics, and supplies in animal?"

6. USDA APHIS Animal Care Policy Manual. Policy #3: Veterinary Care.

7. Drug Compounding Operational Guideline.

8. USP Compounding Compendium. <797> Pharmaceutical Compounding – Sterile Preparations

UCSB Animal Resource Center
Operational Guideline

Title: Drug Compounding

Purpose:

Compounding refers to any manipulation of a pharmaceutical-grade[1] drug beyond that stipulated on the drug label. Federal extralabel drug use regulations specifically permit compounding from FDA-approved drugs when a veterinarian believes there is a need to alter the approved drug to adequately medicate a non-food animal with a diagnosed medical condition.[2] Since almost none of the drugs that are administered to laboratory animals in our Animal Care and Use Program (ACUP) are formulated for those species, extralabel drug use is almost always required. This Operational Guideline describes acceptable

methods for compounding and storing our most commonly used drugs, and establishes a quality assurance process for verifying drug stability and sterility, when needed. This Operational Guideline does not set standards for all the drugs used in our ACUP; however, the Operational Guideline can, in principle, be applied to most pharmaceutical-grade drugs. Contact the Campus Veterinarian if/when you need to develop a compounding procedure for a new drug.

Procedures:

Note: The procedures described below require that you use appropriate precautions to prevent microbial contamination, including using only sterile materials (e.g., needles and syringes) and solutions (e.g., diluents), and manipulating all sterile products aseptically.

I. FDA-approved drugs that require reconstitution prior to IV administration.

1. Brevital® (methohexital sodium)

a. Start with an FDA-approved drug formulation, and prepare a 1% solution (10 mg/ml methohexital) according to the drug monograph (a.k.a., product insert).

   i. Add 50 ml of Sterile Water for Injection to the vial containing the powdered (500 mg) of Brevital®. Do not use a diluent with a preservative (i.e., don't use a bacteriostatic diluent). Do not use a non-sterile diluent (i.e., nanopure water).

   ii. Shake gently to reconstitute

b. Any withdrawal of the drug solution from the original bottle must be performed aseptically – the septum must be wiped with alcohol, and the drug must be removed with a sterile needle and syringe. Any unused drug must be discarded and no drug or other solution must ever be added to the drug vial after initial preparation.

c. According to the drug manufacturer, this drug solution should be stored in the original bottle, at room temperature, and discarded by 24 hrs. after preparation. Alternatively, and according to published[3] quality assurance testing results, the drug solution may be stored refrigerated for up to 42 days (6 weeks). Any storage or use beyond that point requires testing to verify sterility and drug stability.

d. The IACUC will need to verify drug stability and sterility for the following storage and use conditions. Please contact the ARC to arrange for this QA testing.

   i. Storage at cold temperatures (refrigerated) with occasional aseptic removal for drug aliquots for up to 6 months.

   ii. Any removal of the drug from the original vial must be performed aseptically – the septum must be wiped with alcohol, and the drug must be removed with a sterile needle and syringe. Any unused drug is discarded and no drug or other solution is ever added to the drug vial after initial preparation.

e. Label the drug bottle with the following information.

   i. Name of the drug (the original label on the bottle already should contain this information).

ii. Beyond-use date (e.g., 42 days from the date of preparation).

2. Cefazolin catheter lock solution for rats with chronic indwelling venous catheters

a. Start with an FDA-approved drug formulation, and reconstitute according to the drug monograph.

i. Add 2.5 ml of Sterile Water for Injection to the vial containing the powdered (1 g) cefazolin. Do not use a diluent with a preservative (i.e., don't use a bacteriostatic diluent). Do not use a non-sterile diluent (i.e., nanopure water).

ii. Shake gently to reconstitute.

iii. The reconstituted solution will contain approximately 334 mg cefazolin/ml.

b. For intravenous administration, this drug must be diluted with Sterile Water for Injection as follows:

i. Use an alcohol prep swab to disinfect the septum of the cefazolin bottle, and then withdraw 2.5 ml of the cefazolin solution (334 mg/ml) with a sterile needle and syringe.

ii. Transfer the cefazolin solution into a 10 ml Sterile Empty Vial (Hospira Inc, Lake Forest, IL; List #5816-11; HenrySchein SKU 009177).

iii. Transfer 5.275 ml of Sterile Water for Injection into the 10 ml Sterile Vial containing the cefazolin. Use a new sterile needle and syringe, and disinfect the septum on the Sterile Water for Injection bottle.

iv. Transfer 0.575 ml of Heparin solution (1000 U/ml) into the 10 ml Sterile Vial containing the cefazolin. Use a new sterile needle and syringe, and disinfect the septum on the heparin vial.

v. The mixture now contains 100 mg/ml cefazolin, and ~70 U/ml heparin.

c. This drug mixture should be stored protected from light (e.g., wrapped in foil), at cold temperatures (refrigerated), and any unused drug must be discarded by 72 hrs. after preparation. Any storage beyond that point requires testing to verify sterility and drug stability.

d. The IACUC will verify drug stability and sterility for the following storage and use conditions. Please contact the ARC to arrange for this QA testing.

i. Storage at cold temperatures (refrigerated) with occasional aseptic removal for drug aliquots for up to 10 days.

ii. Any removal of the drug from the original vial must be performed aseptically – the septum must be wiped with alcohol, and the drug must be removed with a sterile needle and syringe. Any unused drug is discarded and no drug or other solution is ever added to the drug vial after initial preparation.

e. Label the drug vial with the following information.

i. Name of the drugs (cefazolin and heparin) and their concentrations (100 mg/ml and 70 IU/ml).

ii. Beyond-use date (i.e., 3 or 10 days from the date of preparation).

II. **FDA-approved drugs that require dilution prior to administration to a small (size) laboratory animal species (i.e., rats and/or mice).**

1. Ketamine:Xylazine mixture for laboratory rats and laboratory mice

a. Start with an FDA-approved ketamine and xylazine drug formulation each of 100 mg/ml concentration.

b. Use an alcohol prep swab to disinfect the septum of the xylazine bottle, and then withdraw:

i. Rat formulation: 1 ml of the xylazine solution (100 mg/ml) with a sterile needle and syringe.

ii. Mouse formulation: 0.1 ml of the xylazine solution (100 mg/ml) with a sterile needle and syringe.

c. Transfer the xylazine solution into a 10 ml Sterile Empty Vial.

d. Use an alcohol prep swab to disinfect the septum of the ketamine bottle, and then withdraw:

i. Rat formulation: 7.5 ml of the ketamine solution (100 mg/ml) with a new sterile needle and syringe.

ii. Mouse formulation: 1 ml of the ketamine solution (100 mg/ml) with a new sterile needle and syringe.

e. Transfer the ketamine solution into the 10 ml Sterile Empty Vial containing the xylazine solution.

f. For the mouse formulation, transfer 8.9 ml of 0.9% Sodium Chloride Injection into the 10 ml Sterile Vial containing the ketamine:xylazine mixture. Use a new sterile needle and syringe, and disinfect the septum on the Sterile Chloride Injection bottle.

g. The final drug concentration in the respective rat and mouse formulations should be:

i. Rat formulation: The mixture now contains 11.76 mg/ml xylazine, and 88.23 mg/ml ketamine (i.e., a 1:7.5 mixture of xylazine:ketamine).

ii. Mouse formulation: The mixture now contains 1 mg/ml xylazine, and 10 mg/ml ketamine (i.e., a 1:10 mixture of xylazine:ketamine)

h. This procedure represents a low-risk level compounded sterile preparation[4], and in the absence of passing a sterility test, this drug may be stored for up to 48 hours at room temperature. This drug mixture should be stored protected from light (e.g., wrapped in foil).

i. Label the drug vial with the following information.

   i. Name of the drug mixture and drug ratio.

   ii. Beyond-use date (i.e., 2 days from the date of preparation).

2. Acepromazine (PromAce®)

a. Start with an FDA-approved acepromazine maleate injectable formulation of 10 mg/ml. This formulation can be used for treating laboratory rats without any compounding (no dilution needed). For laboratory mice, dilute this formulation 1:10 as follows.

b. Use an alcohol prep swab to disinfect the septum of the acepromazine vial/bottle, and then withdraw 1 ml of the solution with a sterile needle and syringe.

c. Transfer the acepromazine solution into a 10 ml Sterile Empty Vial.

d. Add 9 ml of Bacteriostatic Saline to the Sterile Empty Vial containing buprenorphine.

i. Use a sterile needle and syringe to withdraw this diluent solution from a new sterile vial/bottle of Bacteriostatic Saline.

e. This new drug formulation procedure represents a low-risk of contamination, and in the absence of passing a sterility test, this drug should only be stored for no more than 14 days at cold temperature.

f. Label the drug vial with the following information.

   i. Name of the drug (i.e., acepromazine) and concentration (1 mg/ml).

   ii. Beyond-use date (i.e., 14 days from the date of preparation for the diluted formulation).

3. Buprenorphine-HCl

a. Start with an FDA-approved buprenorphine drug formulation of 0.3 mg/ml. This formulation can be used for treating laboratory rats without any compounding (no dilution needed). For laboratory mice, dilute this formulation 1:10 as follows.

b. Use an alcohol prep swab to disinfect the septum of the buprenorphine vial/bottle, and then withdraw 1 ml of the buprenorphine solution (0.3 mg/ml) with a sterile needle and syringe.

c. Transfer the buprenorphine solution into a 10 ml Sterile Empty Vial.

d. Add 9 ml of Bacteriostatic Saline to the Sterile Empty Vial containing buprenorphine.

   i. Use a sterile needle and syringe to withdraw this diluent solution from a new sterile vial/bottle of Bacteriostatic Saline.

e. This new drug formulation procedure represents a low-risk of contamination. Based on published testing results for an identical preparation method, this drug should only be stored for up to 180 days at room temperature.[5]

f. Label the drug vial with the following information.

i. Name of the drug (i.e., buprenorphine) and concentration (0.3 mg/ml, or 0.03 mg/ml).

ii. Beyond-use date (i.e., 180 days from the date of preparation for the diluted formulation).

4. Banamine® (Flunixin meglumine)

a. Start with an FDA-approved Banamine® drug formulation of 50 mg/ml.

b. Use an alcohol prep swab to disinfect the septum of the Banamine® bottle, and then withdraw 1 ml of the Banamine® solution (50 mg/ml) with a sterile needle and syringe. For a mouse formulation, withdraw only 0.1 ml.

c. Transfer the Banamine® solution into a 10 ml Sterile Empty Vial (Hospira Inc., Lake Forest, IL; List #5816-11).

d. Add 9 ml (i.e., 1:10 dilution) of Bacteriostatic Saline to the Sterile Empty Vial containing Banamine®. For a mouse formulation, add 9.9 ml (i.e., 1:100) of Bacteriostatic Saline.

i. Use a sterile needle and syringe to withdraw this diluent solution from a new sterile vial/bottle of Bacteriostatic Saline.

e. This new drug formulation procedure represents a low-risk of contamination, and in the absence of passing a sterility test, this drug should only be stored for no more than 14 days at cold temperature.

f. Label the drug vial with the following information.

i. Name of the drug (i.e., Banamine®) and concentration (5 or 0.5 mg/ml).

ii. Beyond-use date (i.e., 14 days from the date of preparation).

5. Meloxicam (Metacam®)

a. Start with an FDA-approved drug formulation of 5 mg/ml meloxicam. Once broached (first puncture of bottle septum), product may be stored at temperatures between 20-25°C (68-77°F) for up to 6 months. This solution can be used for treating laboratory rats without any compounding (no dilution needed). For laboratory mice, dilute this formulation 1:10 as follows.

b. Use an alcohol prep swab to disinfect the septum of the meloxicam bottle, and then withdraw 1 ml of the meloxicam solution (5 mg/ml) with a sterile needle and syringe.

c. Transfer the meloxicam solution into a 10 ml Sterile Empty Vial (Hospira Inc., Lake Forest, IL; List #5816-11).

d. Add 9 ml of Bacteriostatic Saline to the Sterile Empty Vial containing meloxicam.

i. Use a sterile needle and syringe to withdraw this diluent solution from a new sterile vial/bottle of Bacteriostatic Saline.

e. This new drug formulation procedure represents a low-risk of contamination, and in the absence of passing a sterility test, this drug should only be stored for up to 14 days at cold temperature.

f. Label the drug vial with the following information.

   i. Name of the drug (i.e., meloxicam) and concentration (0.5 mg/ml).

   ii. Beyond-use date (i.e., 14 days from the date of preparation).

6. Carprofen (Rimadyl®)

a. Start with an FDA-approved drug formulation of 50 mg/ml carprofen. Store this 20 ml bottle at 2°–8°C (36°–46°F). Once broached (first puncture of bottle septum), product may be stored at temperatures up to 25°C (77°F) for 28 days.

b. Use an alcohol prep swab to disinfect the septum of the carprofen bottle, and then withdraw 1 ml of the solution with a sterile needle and syringe.

c. Transfer the carprofen solution into a 10 ml Sterile Empty Vial (Hospira Inc., Lake Forest, IL; List #5816-11).

d. Add 9 ml of Bacteriostatic Saline to the Sterile Empty Vial containing the carprofen.

   i. Use a sterile needle and syringe to withdraw this diluent solution from a new sterile vial/bottle of Bacteriostatic Saline.

e. This new drug formulation procedure represents a low-risk of contamination, and in the absence of passing a sterility test, this drug should only be stored for up to 14 days at cold temperature.

f. Label the drug vial with the following information.

   i. Name of the drug (i.e., carprofen) and concentration (5 mg/ml).

   ii. Beyond-use date (i.e., 14 days from the date of preparation).

7. Gentamicin catheter lock solution for rats with chronic indwelling venous catheters

a. Use the FDA-approved formulation of 40 mg/ml gentamicin for IV administration. ***Do not use a formulation that is not intended for IV administration (e.g., uterine flush formulation for large animals).*** This formulation should be diluted (1:20) as follows.

b. For intravenous administration, this drug should be diluted with 0.9% Sodium Chloride Injection as follows:

   i. Use an alcohol prep swab to disinfect the septum of the gentamicin vial, and then withdraw 0.5 ml of the gentamicin solution (40 mg/ml) with a sterile needle and syringe.

   ii. Transfer the gentamicin solution into a 10 ml Sterile Empty Vial (Hospira Inc., Lake Forest, IL; List #5816-11; HenrySchein SKU 009177).

   iii. Transfer 8.8 ml of 0.9% Sodium Chloride Injection into the 10 ml Sterile Vial containing the gentamicin. Use a new sterile needle and syringe, and disinfect the septum on the Sterile Chloride Injection bottle.

iv. Transfer 0.7 ml of Heparin solution (1000 U/ml) into the 10 ml Sterile Vial containing the gentamicin. Use a new sterile needle and syringe, and disinfect the septum on the heparin vial.

v. The mixture now contains 2 mg/ml gentamicin, and 70 U/ml heparin.

c. This drug formulation procedure represents a low-risk of contamination, and in the absence of passing a sterility test, this drug should only be stored for up to 14 days at cold temperature.

d. Label the drug vial with the following information.

i. Name of the drug (i.e., gentamicin) and concentration (2 mg/ml).

ii. Beyond-use date (i.e., 14 days from the date of preparation).

8. Enrofloxacin (Baytril®)

a. Use the FDA-approved formulation of 22.7 mg/ml Baytril® for SC administration. This formulation can be used for treating laboratory rats without any compounding (no dilution needed). For laboratory mice, dilute this formulation 1:10 as follows.

b. Use an alcohol prep swab to disinfect the septum of the Baytril® bottle, and then withdraw 1 ml of the Baytril® solution (22.7 mg/ml) with a sterile needle and syringe.

c. Transfer the Baytril® solution into a 10 ml Sterile Empty Vial (Hospira Inc., Lake Forest, IL; List #5816-11).

d. Add 9 ml of 0.9% Sodium Chloride Injection to the Sterile Empty Vial containing lidocaine.

i. Use a sterile needle and syringe to withdraw this diluent solution from a new sterile vial/bottle of Sodium Chloride Injection.

e. This drug formulation procedure represents a low-risk of contamination, and in the absence of passing a sterility test, this drug should only be stored for up to 14 days at cold temperature.

f. Label the drug vial with the following information.

i. Name of the drug (i.e., Baytril®) and concentration (2.27 mg/ml).

ii. Beyond-use date (i.e., 14 days from the date of preparation).

9. Combi-Pen-48® (penicillin G benzathine and penicillin G procaine)

a. Use the FDA-approved formulation of 300,000 IU penicillin G/ml for SC administration. This formulation must be diluted for treating laboratory rats (1:10) or laboratory mice (1:100), as follows.

b. Use an alcohol prep swab to disinfect the septum of the Combi-Pen-48® bottle, and then withdraw 1 ml (rat formulation) or 0.1 ml (mouse formulation) of the Combi-Pen-48® solution (300,000 IU/ml) with a sterile needle and syringe. Make sure to warm the Combi-Pen-48® bottle to room temperature and shake well before withdrawing the solution.

c. Transfer the Combi-Pen-48® solution into a 10 ml Sterile Empty Vial (Hospira Inc, Lake Forest, IL; List #5816-11).

d. Add 9 ml (rat formulation) or 9.9 ml (mouse formulation) of Sterile Water for Injection to the Sterile Empty Vial containing lidocaine.

   i. Use a sterile needle and syringe to withdraw this diluent solution from a new sterile vial/bottle of Sterile Water for Injection.

e. This drug formulation procedure represents a low-risk of contamination, and in the absence of passing a sterility test, this drug should only be stored for up to 14 days at cold temperature (refrigerated).

f. Label the drug vial with the following information.

   i. Name of the drug (i.e., Combi-Pen-48®) and concentration (30,000 or 3,000 IU/ml).

   ii. Beyond-use date (i.e., 14 days from the date of preparation).

10. Euthasol™ (euthanasia solution)

a. Start with the FDA-approved Euthasol™ formulation. This formulation can be used for treating laboratory rats and larger animals (e.g., rabbits) without any compounding (no dilution needed). For laboratory mice, dilute this formulation 1:10 as follows.

b. Use an alcohol prep swab to disinfect the septum of the Euthasol™ bottle, and then withdraw 1 ml of the Euthasol™ solution with a sterile needle and syringe.

c. Transfer the Euthasol™ solution into a 10 ml Sterile Empty Vial (Hospira Inc, Lake Forest, IL; List #5816-11).

d. Add 9 ml of Sterile Water for Injection or 0.9% Sodium Chloride Injection to the Sterile Empty Vial containing lidocaine.

   i. Use a sterile needle and syringe to withdraw this diluent solution (i.e., Sterile Water for Injection or Sodium Chloride Injection) from a new sterile vial/bottle.

e. This procedure represents a low-risk level compounded sterile preparation, and in the absence of passing a sterility test, this drug should only be stored for up to 14 days at refrigerated temperature.

f. Label the Sterile Empty Vial with the following information.

   i. Name of the drug (i.e., Euthasol) and concentration (e.g., 1:10 dilution).

   ii. Beyond-use date (i.e., 14 days from the date of preparation).

III. Pharmaceutical-grade[1] drug or experimental substance that requires reconstitution prior to parenteral (e.g., IV, IP, IM, or SC) administration.

1. Start with a USP-grade chemical, and prepare a drug solution of the desired concentration as follows.

2. If the drug solution is going to be administered IV, or IP, then use Sterile Water for Injection or Sodium Chloride Injection to dissolve the USP-grade chemical powder. If the drug solution is going to be administered SC or IM, then use Bacteriostatic Saline. Do not use a non-sterile diluent (i.e., nanopure water). If the drug requires a different diluent/vehicle, then make sure that this diluent/vehicle is listed and approved on your protocol. Contact the Campus Veterinarian for additional assistance.

3. Transfer the drug solution to a 10 ml Sterile Empty Vial with a multi-use septum (Hospira Inc., Lake Forest, IL; List #5816-11).

    a. Use a sterile syringe to draw up the drug solution.

    b. Place a syringe-top filter (0.2 µm) between the syringe and a sterile needle.

    c. Puncture the septum of the Sterile Empty Vial to and inject the drug solution and into a Sterile Empty Vial.

4. Verification of appropriate storage and beyond-use date requires testing to verify sterility and drug stability. Please contact the ARC to arrange for this QA testing. In the absence of any drug stability and sterility testing, the drug should be prepared fresh each time. However, and in agreement with the USP Compendium[4] recommendation for a high-risk level compounded sterile preparation, the drug solution should only be stored for up to 3 days at refrigerated temperature.

5. Label the Sterile Empty Vial with the following information.

    a. Name of the drug and concentration (e.g., X mg/ml).

    b. Beyond-use date (i.e., 3 days from the date of preparation).

Reference:

1. The definition of pharmaceutical-grade established by the NIH Office of Laboratory Animal Welfare is: "A pharmaceutical-grade substance is any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices (GMP) which is approved, conditionally approved, or indexed by the Food and Drug Administration (FDA) or for which a chemical purity standard has been written or established by a recognized compendia (e.g., United States Pharmacopeia-National Formulary (USP-NF), British Pharmacopeia (BP))."

2. "Compounding: FAQ for Veterinarians" https://www.avma.org/KB/Resources/FAQs/Pages/Compounding-FAQs.aspx

3. Stability of reconstituted methohexital sodium. J Oral Maxillofac Surg. 1994 Apr; 52(4) 393-396.

4. USP Compounding Compendium. <797> Pharmaceutical Compounding – Sterile Preparations.

5. Effects of Time and Storage Conditions on the Chemical and Microbiologic Stability of Diluted Buprenorphine for Injection. J Am Assoc Lab Anim Sci. 2017 Jul 01; 56(4) 457-461.