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| TITLE: Use of Non-Pharmaceutical Grade or Expired Materials | APPROVED: June 20, 2012 |
| IACUC POLICY: 002 REVISION: 2 | REVISED: October 26, 2015 |
| SCOPE: This policy applies to the use of expired drugs or materials, assigning expiration dates and non-pharmaceutical grade compounds. | |
| KEYWORDS: expired materials, expired drugs, terminal use only, expiration dates, non-pharmaceutical grade compounds, Assigning Expiration Dates to Materials Sterilized In-House | |
| Policy Owner: Office of Research Integrity Assurance (ORIA) Georgia Tech Research Corporation (GTRC) | |
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1. BACKGROUND:

The Animal Welfare Act (9 CFR Part 2, subpart C (sections 2.31-2.33) and subpart D (section 2.40)) and Public Health Service (PHS) Policy on the Humane Care and Use of Laboratory Animals require the provision of adequate veterinary care, to be overseen by the Attending Veterinarian and IACUC. The United States Department of Agriculture (USDA) Animal Care Policy #3 (<http://www.aphis.usda.gov/ac/policy3.html>) indicates specifically, "The use of expired medical materials such as drugs, fluids, or sutures on regulated animals is not considered to be acceptable veterinary practice and does not constitute adequate veterinary care, as required by the regulations promulgated under the Animal Welfare Act." The Office for Laboratory Animal Welfare (OLAW) provides similar requirements (<http://grants.nih.gov/grants/olaw/faqs.htm#f5>).

2. POLICIES:

Use of expired anesthetics, analgesics, euthanasia or emergency drugs is unacceptable.

A: Expired Materials other than anesthetics, analgesics, euthanasia or emergency drugs

Expired medical materials (drugs, devices, implants, fluids, sutures, etc.) may only be used on dead or anesthetized animals during terminal procedures from which they will not recover. Expired materials must be labeled and separated from other materials.

Drug Bottles Made In-House

When drugs are aliquoted, diluted or mixed into cocktails or dispensed by the animal facility so that they are no longer in manufacturer's bottles they must be marked with the expiration date of the soonest expiring component, the name of the drug(s) and the concentration(s). These mixtures and aliquots expire on the date of the soonest expiring component unless data indicates otherwise.

Inventory

To assure that expired items are identified in a timely fashion each research group should inspect their animal drug and material storage areas monthly.

Aseptic Technique When Using Septum Vials

Needles, syringes and vials used for sterile injectable drugs must be sterile. It is recommended that sterile injectable drugs be used even in non-survival procedures as rapidly occurring inflammatory reactions to microbes can affect research outcomes. Used or contaminated (by touching anything non-sterile) needles must never be inserted through the septum of a sterile drug vial. The septum of sterile drug vials should be wiped with alcohol before needle insertion.

Expiration of Single Dose Vials and Other Pharmaceuticals Not Containing Preservatives

A few drugs and most fluids stocked by the PRL contain no preservatives or bacteriostatic agents. Most of these are manufactured and labeled for the human market as Single Dose Vials (SDV). Because most animals used in the PRL are smaller than humans, SDV often contain many animal doses within one vial. Drug and fluid containers that do not contain preservatives may be repeatedly punctured and used until their expiration date unless data suggest harm will come from this practice, holes can be seen in the septum, precipitates have formed in the bottle or contamination or unaccounted discoloration of the bottle has occurred. Following the aseptic technique above helps insure continued sterility of the bottle despite absence of bacteriostatic agents. Fluids in screw capped bottles, usually called and labeled "for irrigation," must be used on the day they are opened.

Items Sterilized In-House

Items sterilized in-house must have an external process indicator (e.g., autoclave or ethylene oxide tape). Cloth-wrapped or paper and plastic wrapped items sterilized in house are considered sterile until or unless the package is compromised by opening, wetting or damage. The function of autoclaves used to sterilize surgical items must be tested at least once per month with commercially made spores.

B. Pharmaceutical Grade Drugs

The 8th edition of the Guide for the Care & Use of Laboratory Animals states "The use of non-pharmaceutical grade chemicals or other substances ensures that toxic or unwanted side effects are not introduced into studies conducted with experimental animals. They should therefore be used, when available, for all animal-related procedures (USDA 19977b)." The 2015 revised USDA Animal Care Policy Manual, Policy #3, states "Pharmaceutical-grade substances are expected to be used whenever they are available, even in acute procedures." It should also be noted, according to OLAW, AAALAC and the USDA, cost-savings alone is not sufficient justification for using a non-pharmaceutical-grade substance in a regulated species; 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.

OLAW guidance defines pharmaceutical grade as "a drug, biologic, or reagent that is approved by the Food and Drug Administration (FDA) or for which a chemical purity standard has been established by the United States Pharmacopeia-National Formulary (USP-NF), or British Pharmacopeia. Reagents are not drugs. Drugs are manufactured by a pharmaceutical producer under Good Manufacturing Practices and approved by the FDA." Historically, substances administered to research animals have been:

Formulated, bottled and labeled for administration to animals or people by a

- 1) pharmaceutical company
- 2) compounding pharmacy
- 3) chemical company

Or

- 4) formulated by researchers from non-sterile or sterile powders or solutions obtained from a chemical company or compounded in a research laboratory

Rather than deciding whether each item above falls under the definition of pharmaceutical grade, the GT IACUC has determined that to maximize animal welfare, sterility, purity, safety and reproducibility of research results substances to be administered to animals used in research or teaching must be obtained from a source as high up on the above list as possible. If there is concern that a preservative or other additive in a formulation from high on the list will affect the research, an appropriate vehicle control should be used in a control group.

If the last means above is approved, toxic impurities must be minimized and the highest purity compound available used. In addition, when applicable diluents from a pharmaceutical company or pharmacy must be used, and then the solution must be passed through a 0.22 micron filter, stored in a sterile vial. Drugs to be used non-sterile or given orally or added to aquatic habitats need not be sterile or diluted with pharmaceutical grade substances. Item 4 drugs expire 90 days from mixing unless data indicate otherwise.

Approving Formulations from Chemical Companies or Formulated in Research Laboratories

The following are some examples that might be reasonable for the IACUC to approve substances from 3 or 4 above.

- The needed drug is unavailable or is not consistently available from a pharmaceutical company or pharmacy.
- Although an equivalent drug is available from a pharmaceutical company or pharmacy, the chemical-grade reagent is required to replicate methods from previous studies because results will be directly compared to those previous studies. This does not apply to drugs used for anesthesia, analgesia and euthanasia unless data indicate a reason for concern.
- Although a drug from a pharmaceutical company or pharmacy is available, a greater concentration or different formulation is required.
- The available drug from a pharmaceutical company or pharmacy does not meet the non-toxic vehicle requirements for the specified route of administration.

3. RESPONSIBILITIES:

- A. GT IACUC - review protocols and modifications to protocols to ensure consistency with the provisions of this policy. Inspect storage of drugs and materials on semi-annual IACUC inspections.
- B. GT ORIA - provide resources and guidance to the IACUC, animal research investigators, and care staff on current regulatory requirements involving the use of expired drugs or materials.
- C. PIs and research team members - ensure that drugs and materials are used and stored in a way that meets the provisions described in this policy.

4. REFERENCES:

OLAW FAQ #5: May investigators use expired pharmaceuticals, biologics, and supplies in animals?
http://grants.nih.gov/grants/olaw/faqs.htm#useandmgmt_5

USDA Animal Care Policy Manual, Animal Care Resource Guide, Issue Date: October 16, 2015
https://www.aphis.usda.gov/animal_welfare/downloads/Animal%20Care%20Policy%20Manual.pdf

OLAW Seminar Series: Use of Non-Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals - March 1, 2012. http://grants.nih.gov/grants/olaw/educational_resources.htm

US Pharmacopeia (USP) and the National Formulary (NF) combined standards compendia available at <http://www.usp.org/usp-nf>.

OLAW Webinar Transcript with Additional Answers to Questions Submitted After the Webinar
http://grants.nih.gov/grants/olaw/120301_seminar_transcript.pdf

Guide for the Care and Use of Laboratory Animals, Eighth Edition, 2011, Animal Care and Use Program: Page 31; Use of Non-Pharmaceutical Grade Chemicals and Other Substances;
<http://www.nap.edu/read/12910/chapter/3#31>

REVISION HISTORY:

| Revision Number | Summary of Revisions | Revision Date |
|------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------|
| 1 | Reference update and formatting | March 10, 2015 |
| 2 | Reference update and clarification regarding the non-use of non-pharmaceutical grade in all animal-related procedures. | October 26, 2015 |