

TITLE: Use of Non-Pharmaceutical Grade or Expired Materials	APPROVED: June 20, 2012
IACUC POLICY: 002 REVISION: 4	REVISED: November 7, 2023
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)	
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1. BACKGROUND:

The *USDA Animal Welfare Act* includes requirements for “adequate veterinary care with the appropriate use of anesthetic, analgesic, tranquilizing drugs, or euthanasia.” The *Guide for the Care and Use of Laboratory Animals* (hereafter, *Guide*) states that anesthetics and analgesics must be used prior to their expiration. In a guidance document, the *Office for Laboratory Animal Welfare (OLAW)* issued similar guidance, stating “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.” *OLAW* guidance also specifies that other types of expired materials should not be used unless the manufacturer can verify efficacy of the expired product, or the investigator can satisfy the IACUC that the expired product will not have a negative effect on animal welfare or study validity. *OLAW* guidance further states “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.”

The *Guide* indicates that pharmaceutical-grade substances should be used for animal procedures whenever available. Otherwise, the proposed use of non-pharmaceutical-grade substances should be justified by the investigator in their IACUC protocol. *OLAW* guidance specifies that available pharmaceutical-grade substances 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.” Though, like the *Guide*, *OLAW* guidance recognizes that there are instances in which it is necessary to use non-pharmaceutical-grade investigational substances, compounded drugs, and/or Schedule I controlled substances to for research purposes.

2. POLICIES:

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

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

Despite the guidance above, the IACUC supports retaining and using certain materials past their expiration date under specific circumstances for the purposes of avoiding complete loss of stock and reducing waste.

Expired pharmaceuticals, including drugs and fluids applied deeper than the skin surface, may only be used on dead or anesthetized animals during terminal procedures from which they will not recover. Expired pharmaceutical materials must be labeled or separated from like materials.

Expired dry goods and solutions that are applied to the skin surface, including gloves, sutures, surgical scrub, needles, syringes, drapes and towels, may be used beyond the manufacturer’s expiration date as follows: (i) use in terminal procedures, (ii) emergency use as determined by the Attending Veterinarian, (iii) use when unexpired materials cannot reasonably be obtained, or (iv) the Attending Veterinarian or the IACUC approves an exception

based upon documented need. Any packages or materials that are degraded, opened, discolored, or show other evidence of unsuitability will be discarded, regardless of the manufacturer's expiration date.

Expired materials will be clearly identified or segregated from unexpired materials. The IACUC maintains control over expired materials by inspecting them semi-annually.

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 animal facility 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 animal facility 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

According to *OLAW* and *AAALAC International* guidance, cost-savings alone is not sufficient justification for using a non-pharmaceutical-grade substance; 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 or research 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 unless, due to extenuating circumstances, the Attending Veterinarian or the IACUC approves an exception. 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.

Sustained-release buprenorphine produced by a compounding pharmacy has been in use in rats and mice at GT since approximately 2011 with no adverse effects after dosages and timing of administration were determined. An *FDA*-indexed alternative or alternatives has been marketed intermittently since then. *FDA* indexing means safety and effectiveness have been affirmed through an alternative *FDA* review process (e.g., when treating animals representing markets too small to support the costs of the traditional drug approval process). *FDA*-indexed drugs may fall above compounding drugs on the list above. The GT IACUC has determined, however, that use of compounded, sustained-release buprenorphine is acceptable based on long usage history combined with lack of experience with and variable availability of *FDA*-indexed alternatives.

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. Georgia Tech 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. Georgia Tech Office of Research Integrity Assurance (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:

United States Department of Agriculture, Animal Welfare Act, Section 2143.

<https://www.govinfo.gov/content/pkg/USCODE-2013-title7/pdf/USCODE-2013-title7-chap54.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 Substance.

<http://www.nap.edu/read/12910/chapter/3#31>

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

Office of Laboratory Animal Welfare, 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

United States Pharmacopeia (USP) and the National Formulary (NF): combined standards compendia.

<http://www.usp.org/usp-nf>.

Office of Laboratory Animal Welfare, Webinar Transcript with Additional Answers to Questions Submitted After the Webinar. http://grants.nih.gov/grants/olaw/120301_seminar_transcript.pdf

AAALAC International, FAQ #9: Non-Pharmaceutical-Grade Compounds.

<https://www.aaalac.org/accreditation-program/faqs/#B9>

Federal Drug Administration, Drug Indexing.

<https://www.fda.gov/animal-veterinary/minor-use/minor-species/drug-indexing>

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 22, 2015
3	Removal of outdated USDA Animal Care Policy 3 and clarifications regarding of expired material use and levels of pharmaceutical grade	April 26, 2021

4	Removal of outdated animal facility name (“PRL”)	November 7, 2023
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