



IACUC Guidance:	TAMU-G-010	Title:	Guidelines for the Use of Pharmaceutical and Non-Pharmaceutical Grade Drugs and Compounds
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Location	Effective Date	Review By
College Station/Dallas/Galveston/Kingsville	06/01/2024	05/31/2027
Houston	07/01/2024	05/31/2027

1. PURPOSE

- 1.1. To outline the expectations for the use of pharmaceutical and non-pharmaceutical grade drugs and compounds in experimental animals.

2. SCOPE

- 2.1. Applies to vertebrate animals used for research, teaching, or other purposes under the oversight of the Texas A&M University IACUC.
- 2.2. This Guidance includes anesthetics, analgesics, and any substances administered experimentally, and applies to non-survival as well as long-term studies.
- 2.3. See TAMU-G-026 for guidance related to chemicals used for sanitation purposes.
- 2.4. See TAMU-G-024 for guidance related to the use of expired medical materials.

3. RESPONSIBILITY

- 3.1. The PI must submit a protocol that describes and justifies the proposed use of the drug or chemical formulation, and the IACUC must review and approve the protocol before experiments are carried out.

4. DEFINITIONS AND/OR ACRONYMS

- 4.1. **AUP:** Animal Use Protocol. Document submitted by the PI indicating the housing and procedures involving animals.
- 4.2. Centrally administered support service for animal research and teaching programs at Texas A&M University:
 - 4.2.1. ARU: Animal Resource Unit supports the School of Dentistry vivarium
 - 4.2.2. CMP: Comparative Medicine Program supports the Texas A&M College Station Campus
 - 4.2.3. PAR: Program for Animal Resources supports the Institute of Biosciences and Technology vivarium
 - 4.2.4. PRF: Pharmaceutical Research Facility supports Kingsville Pharmaceutical Science Facility vivarium.
 - 4.2.5. Sea Life: The Sea Life Facility supports the Galveston campus.
- 4.3. **Compounding:** The combining, mixing, or alteration of ingredients of a drug to create a medication tailored to the needs of the individual patient.
- 4.4. **Controlled Substances:** Drugs and other substances that are considered controlled substances under the CSA and divided into five schedules.
- 4.5. **CSA:** Controlled Substances Act
- 4.6. **EHS:** Environmental Health and Safety Department
- 4.7. **FDA:** U.S. Food and Drug Administration
- 4.8. **IACUC:** Institutional Animal Care and Use Committee. Institutional body responsible for ensuring adherence to federal regulation and institutional policy relating to the care and use of animals in teaching, testing and research. Appointed by the Institutional Official.
- 4.9. **Medical Material:** General category which includes but is not limited to drugs administered for clinical or therapeutic purposes, fluids, substances administered for experimental purposes, implantable materials, catheters, sutures, surgical gloves, skin disinfection solution, and other medical devices and medical materials used in or on live vertebrate animals.
- 4.10. **Non-pharmaceutical Grade Substance:** Any active or inactive drug, biologic or reagent, for which a chemical purity standard has not been established by a recognized national or regional pharmacopeia.

- 4.11. **OLAW:** Office of Laboratory Animal Welfare. Provides guidance and interpretation of the Public Health Service (PHS) Policy on the Humane Care and Use of Laboratory Animals (Policy) for PHS-funded research and monitors compliance with the Policy by Assured Institutions.
- 4.12. **Pharmaceutical Grade Substance:** Any active or inactive drug, biologic or reagent, for which a chemical purity standard has been established by a recognized national or regional pharmacopeia (e.g., the U.S. Pharmacopeia (USP), British Pharmacopeia (BP), National Formulary (NF), European Pharmacopoeia (EP), Japanese Pharmacopeia (JP), etc.). The Food and Drug Administration (FDA) maintains a database listing of FDA approved commercial formulations for both FDA approved human drugs (the Orange Book) and veterinary drugs (the Green Book).
- 4.13. **PI:** Principal Investigator. The individual who has ultimate administrative and programmatic responsibility for the design, execution, and management of a project utilizing vertebrate animals.
- 4.14. **Tribromoethanol (TBE):** is an injectable anesthetic previously manufactured under the trade name Avertin®. However, this product is no longer available in pharmaceutical grade. In addition, TBE can cause several deleterious effects when administered to animals.
- 4.15. **USDA:** United States Department of Agriculture. USDA Animal Care, a unit under the Animal and Plant Health Inspection Service, administers the Animal Welfare Act (AWA) and associated Animal Welfare Act Regulations (AWAR).
- 4.16. **USDA Covered Species:** A term that refers to animals whose care is governed by the Animal Welfare Act. USDA-Covered Species include all live or dead warm-blooded animals used in research except birds bred in captivity, rats of the genus *Rattus*, and mice of the genus *Mus* bred for research. This also excludes "cold-blooded" animals such as fish, reptiles, and amphibians.

5. GUIDELINES OR PROCEDURE

- 5.1. The use of non-pharmaceutical grade substances in animal-based research requires prior IACUC approval and must be based on either:
 - 5.1.1.1. Unavailability of an acceptable veterinary or human pharmaceutical-grade compound
 - 5.1.1.2. Scientific necessity
 - 5.1.2. Additional factors the Guide and OLAW state that must be addressed include:
 - 5.1.2.1. Stability, potency, and sterility of formulation,
 - 5.1.2.2. The storage and preparation procedures,
 - 5.1.2.3. How expiration or beyond use dates will be determined.
 - 5.1.3. Any non-FDA approved substance is therefore considered to be non-pharmaceutical grade and requires justification in the IACUC application. These substances are available in a spectrum of quality and consistency. The following order of choice should be applied:
 - 5.1.3.1. Drug compounded from an FDA-approved drug, or an active pharmaceutical ingredient manufactured in conformance with current Good Manufacturing Practice and meeting United States Pharmacopeia/National Formulary/British Pharmacopeia (USP/NF/BP) standards. This includes drugs acquired from a Pharmacy Compounding Accreditation Board or FDA-registered compounding pharmacy.
 - 5.1.3.2. USP-grade chemical or substance used to formulate a needed dosage form (e.g., electrolytes, amino acids, DMSO, dextrose, or methylcellulose powder).
 - 5.1.3.3. Non-pharmaceutical grade or non-USP grade compounds: (e.g., analytical, or reagent grade chemicals, such as those from Sigma-Aldrich®; peptides; or oligonucleotides used to compound or formulate a needed dosage form).
 - 5.1.3.4. NOTE: Dilutions or formulation modifications to an FDA-approved veterinary or human drug or biologic also require IACUC approval to ensure safety, efficacy, proper storage, and assignment of expiration dates. Choice of diluent should be discussed with the AV, or designee, particularly when fluid administration has to be balanced in the animal model, such as heart or renal failure.

- 5.2. Pharmaceutical grade drugs are tested for purity to reduce the possibility that they are contaminated with toxic compounds that may harm an animal.
 - 5.2.1. How to determine if your substance is pharmaceutical grade:
 - 5.2.1.1. Presence of an NDC (National Drug Code) number on the box, bottle, or vial (this number is often in small print (<6 point), and may be difficult to read; however, it is a reliable indicator of the substance grade); and
 - 5.2.1.2. Presence of an expiration date; and
 - 5.2.1.3. Presence of a lot number; and
 - 5.2.1.4. Purchased from a USDA licensed vendor or pharmacy or listed as “pharmaceutical grade” in the vendor catalog.
 - 5.2.1.5. Description on box, bottle, or vial stating the product is FDA approved, or the presence of the USP insignia.
 - 5.2.2. Compounding. The IACUC considers dilutions/reconstitutions/mixtures/compounding to be equivalent to pharmaceutical grade as long as:
 - 5.2.2.1. All ingredients within the solution/mixture are pharmaceutical grade.
 - 5.2.2.2. Sterility (sterile glass tubes/bottles with rubber access stoppers) and proper storage must be followed during compounding and use.
 - 5.2.2.3. Dilutions should be per manufacturer’s specification as beyond use date can be affected by choice of diluent.
 - 5.2.2.4. All dilutions or mixtures must be minimally labeled with:**
 - 5.2.2.4.1. Name of substance(s)
 - 5.2.2.4.2. Concentration
 - 5.2.2.4.3. Preparation date/Expiration date (note: expiration date must be included for clinical drugs and compounds administered to USDA covered species)
 - 5.2.2.5. Compound Preparation and Storage Methodologies
 - 5.2.2.5.1. Compounds for injection must be prepared in a sterile manner:
 - 5.2.2.5.1.1. Use sterile constituents.
 - 5.2.2.5.1.2. Mix solutions using sterile technique (hood, open flame, etc.)
 - 5.2.2.5.1.3. Pass solution through a syringe filter (0.22um) at the time of preparation into a sterile container (rubber-capped glass bottle)
 - 5.2.2.5.1.4. Maintain proper storage conditions for the constituents of the solution (proper temperature and light)
 - 5.2.2.5.1.5. Discard if solution is cloudy, precipitated or discolored.
- 5.3. Non-Pharmaceutical Grade Drug Use
 - 5.3.1. Most drugs are formulated to contain excipients that are safe for clinical use but may interfere with experimental objectives. If the excipients do not confound the study, then the drug should be obtained from a veterinary supply house or from a pharmaceutical supplier licensed by the FDA. If excipients interfere with the experimental objectives or if the chemical is not approved for clinical use, the investigator is allowed to formulate the drug or chemical provided that purity and stability of the drug is maintained.
 - 5.3.2. Controlled scientific studies may require a control group dosed with the vehicle only, and the vehicle may not be readily available.
 - 5.3.3. Some studies will use novel chemicals or mixtures of chemicals either synthesized or isolated from natural sources. These chemicals should be of the highest purity attainable (either from commercial sources or from laboratory procedures during their preparation) and formulated in an appropriate manner for a specific route of administration.
 - 5.3.4. When new drug or chemical formulations are proposed, the IACUC may consider factors such as the grade, purity, sterility, pH, pyrogenicity, osmolality, stability, site and route of administration, formulation, compatibility, and the pharmacokinetics of the chemical or substance to be administered.

- 5.3.5. Investigators are encouraged to contact a veterinarian regarding the preparation of the drug before AUP submission to the IACUC, but in some instances a pharmacologist or toxicologist consult may be warranted.
- 5.3.6. Cost savings alone do not adequately justify the use of non-pharmaceutical-grade compounds in animals. 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.
- 5.3.7. Although the potential animal welfare consequences of complications are less evident in non-survival studies, the scientific issues remain the same, and the principles and need for professional judgment outlined above still apply.

5.4. Expiration, Labelling and Segregation of Expired Drugs and Compounds:

- 5.4.1. **Expired anesthetic, analgesic, euthanasia, or emergency drugs cannot be used on or administered to live animals under any circumstances.**
 - 5.4.1.1. See TAMU-G-024 for more information on the use of expired medical materials other than those listed above.
 - 5.4.1.2. All expired drugs must be segregated and clearly marked “EXPIRED” on or before their date of expiration.
- 5.4.2. **Inventory:** The IACUC recommends that each laboratory establish an inventory procedure to facilitate the identification, segregation and discarding of expired drugs and compounds (also applies to other medical materials). Expired drugs/compounds not immediately disposed of must be segregated from in-date stock and clearly marked “EXPIRED – not for use in live animals”.
 - 5.4.2.1. See TAMU-G-024 for additional labeling requirements for expired medical materials maintained for IACUC approved activities in live animals.
 - 5.4.2.2. Consider assigning the inventory responsibilities to one specific individual, with another individual assigned as backup.
 - 5.4.2.3. Establish an inventory system that minimizes the volume of drugs or compounds (or medical supplies) on hand.
 - 5.4.2.4. Perform frequent checks (i.e.: monthly) of your inventory and segregate, label, and discard all expired drugs or compounds (also applies to other medical materials).
 - 5.4.2.5. Dispose of drugs/chemicals per manufacturer requirements and institutional standards. Consult EHS for assistance in determining the appropriate mechanism of disposal when unsure.
 - 5.4.2.6. Expired controlled substances must be kept secure awaiting reverse distribution. Segregation may be in the form of a separate box or bag within the same storage location as in-date stock with expiration labelling on both the storage container and individual drug containers (i.e.: boxes, bottles, etc.). PIs are encouraged to contact EHS for assistance with reverse distribution.
- 5.4.3. **Drugs/Compounds with manufacturer provided expiration date:**
 - 5.4.3.1. All FDA-approved drugs and fluids are imprinted with an expiration date. Beyond this date, the manufacturer does not guarantee the sterility, safety, or stability of the item.
 - 5.4.3.2. The date of expiration is either the month, day, year imprinted by the manufacturer (in whatever order); or the last date of the specified month when manufacturer does not include the day of expiration.
 - 5.4.3.3. If a drug is aliquoted unchanged into a sealed, sterile container (e.g., a red-top vacutainer, an empty sterile vial), it maintains the original expiration date. Note: The expiration date may be altered if the drug was originally packaged in a special atmosphere such as argon or nitrogen. Refer to the manufacturer for guidance on establishing a new expiration date.
 - 5.4.3.4. In select cases the manufacturer may verify sterility, safety, or stability of a drug/compound beyond the imprinted date of expiration. Written documentation of this verification must be maintained by the PI when drugs/compounds are used beyond the imprinted expiration date.
- 5.4.4. **No manufacturer provided expiration date:**

5.4.4.1. Drugs or compounds without expiration dates should be dated upon receipt. The investigator should determine the stability of the drug to establish a reasonable shelf-life. This is commonly obtained from the manufacturer, and for most stable organic compounds the shelf-life is up to three years. If stability is unknown, the drug should not be used beyond one year.

5.4.5. Expiration of drug and compound dilutions/reconstitutions/mixtures/compounds

5.4.5.1. Drugs and compounds that are altered from their original form (e.g., diluted, reconstituted, or mixed with other drugs) do not necessarily keep their original expiration dates. Dilution, mixing, etc. may cause the drugs to lose potency, degrade or precipitate.

5.4.5.2. For dilutions and mixtures of drugs removed from the manufacturer's primary packaging and placed into a sealed, sterile container, best practice is to discard after one month from the date of preparation or at the earliest expiration date of the component drugs, whichever comes first, unless the manufacturer specifies a longer or shorter dilution shelf-life. The following exceptions are noted:

5.4.5.2.1. Buprenorphine or meloxicam diluted with sterile saline, stored in the dark and maintained sterile expire in 90 days.

5.4.5.2.2. Ketamine and xylazine mixtures, stored in the dark and maintained sterile expire in 90 days.

5.4.5.2.3. As even fresh solutions of Tribromoethanol can cause lethality, the IACUC suggests best practice is to discard working solutions after two weeks.

5.4.6. Expiration of fluids administered intravenously (IV)

5.4.6.1. IV fluid bags maintained aseptically for subcutaneous use in multiple animals (e.g., normal saline, Lactated Ringer's) expire 30 days after opening when kept at room temperature.

5.4.6.2. IV fluids used clinically are patient-specific and will only be used for that patient, any excess will be discarded.

6. RECORDS

6.1. Research records, including medical records, must be maintained consistent with Texas A&M University Standard Administrative Procedures (SAPS) 15.99.03.M1.03. and 29.01.03.M0.01.

7. EXCEPTIONS

7.1. The PI may request an exception to the above standards by describing the departure in the AUP.

7.2. For programmatic exceptions, the facility director or manager may submit a request for the exception using TAMU-F-013.

8. REFERENCES, MATERIALS, AND/OR ADDITIONAL INFORMATION

8.1. References

8.1.1. FDA [Orange Book](#) – Approved Human Drug Products with Therapeutic Equivalence Evaluations

8.1.2. FDA [Green Book](#) – Approved Animal Drug Products

8.1.3. [FDA Drug Shortages](#)

8.1.4. OLAW FAQ F.4. *May investigators use non-pharmaceutical-grade substances in animals?*

8.1.5. [Demystifying Material Grades for Your Laboratory](#)

8.1.6. [#242 In-Use Stability Studies and Associated Labeling Statements for Multiple-Dose Injectable Animal Drug Products Guidance for Industry](#)

8.1.7. Efficacy and Safety of Stored and Newly Prepared Tribromoethanol in ICR Mice. Contem Top Lab Animal Sci, 2005. 44(1): 17-22.

8.1.8. An Evaluation of Preparation Methods and Storage Conditions of Tribromoethanol. Contem Top Lab Animal Sci, 2005. 44(1): 11-16.

- 8.1.9. Denherder, J., et al. Effects of time and storage conditions on the chemical and microbiological stability of diluted buprenorphine for injection. J AM Assoc Lab Anim Sci.2017 56(4):457-461.
- 8.1.10. Dodulet-Devillers, A., et al. Assessment of stability of ketamine-xylazine preparations with or without acepromazine using high performance liquid chromatography-mass spectrometry. Can J Vet Res. 2016. 80(1):86-89.
- 8.1.11. Hawkins, M., et al. Drug distribution and stability in extemporaneous preparations of meloxicam and carprofen after dilution and suspension at two storage temperatures. J AM Vet Med Assoc. 2006. 229(6): 968-974.
- 8.1.12. Matthews KA, Taylor DK. Assessment of sterility in fluid bags maintained for chronic use. J Am Assoc Lab Anim Sci. 2011;50(5):708–712.
- 8.1.13. Taylor, B., et al. Beyond-use dating of extemporaneously compounded ketamine, acepromazine, and xylazine: safety, stability, and efficacy over time. J AM Assoc Lab Anim Sci. 2009. 48 (6):718-26.

8.2. Resources

- 8.2.1. Disposal of Substances - For proper disposal of controlled substances, hazardous waste (e.g., chemical, microbiological, animal products, human blood, etc.), go to the [EHS website](#), or call (979) 845-2132.
- 8.2.2. For assistance finding sources for veterinary pharmaceuticals, contact:
 - 8.2.2.1. [CMP](#) at 979-845-7433
 - 8.2.2.2. ARU: at (214) 828-8149
 - 8.2.2.3. [PAR](#): at (713) 677-7471
 - 8.2.2.4. PRF: at (361) 221-0770

8.3. [IACUC/AWO Referenced Documents](#): (requires TAMU NetID authentication)

- 8.3.1. AWO-O-005 Expired Drug Label
- 8.3.2. TAMU-G-002 Guidelines on the use of Anesthesia and Analgesia
- 8.3.3. TAMU-G-024 Guidelines for the Use of Expired Medical Materials
- 8.3.4. TAMU-G-026 Guidelines for the Evaluation of Sanitation Practices

8.4. TAMU Division of Research [Controlled Substances Guidelines](#)

8.5. Acknowledgements

- 8.5.1. This document contains content that was adapted from materials obtained from the Universities of Michigan and Washington State and the University of Texas at Austin.

9. HISTORY

Effective Date	Version #	Description
08/15/2019	000	College Station/Galveston: new format and updated content
07/01/2020	001	Houston/Kingsville: new format and updated content, replaced IBT-201.03; reviewed & approved by email
08/18/2020	002	Dallas: new format and updated content, replaced CD-201.02. Added 5.5.3.2.
06/01/2021	003	College Station/Galveston: Renewal document; updated definitions and references; additional guidance re: dilutions and their expirations
07/01/2021	004	Houston/Kingsville: Renewal document; updated definitions and references; additional guidance re: dilutions and their expirations
07/20/2021	005	Dallas: Renewal document; updated definitions and references; additional guidance re: dilutions and their expirations
03/24/2022	006	College Station/Dallas/Galveston: Merging of Dallas animal care and use program with College Station/Galveston
10/20/2022	007	College Station/Dallas/Galveston/Kingsville: Merging of Kingsville animal care and use program with College Station/Dallas/Galveston.



03/01/2024	008	College Station/Dallas/Galveston/Kingsville: Renewal; updated definitions and references sections; clarified aseptic storage, extended expiration for specific mixtures, updated best practices, removed Dallas-specific information; added exception section. Reviewed and approved via TEAMS.
04/01/2024	009	Houston: Renewal; updated definitions and references sections; clarified aseptic storage, extended expiration for specific mixtures, updated best practices, removed Dallas-specific information; added exception section. Reviewed and approved via TEAMS.
06/01/2024	010	College Station/Dallas/Galveston/Kingsville: Renewal; updated scope, definitions, procedures, and references sections to incorporate expiration related text from TAMU-G-024; addition of records section.
07/01/2024	011	Houston: Renewal; updated scope, definitions, procedures, and references sections to incorporate expiration related text from TAMU-G-024; addition of records section.