DOWNSTATE
HEALTH SCIENCES UNIVERSITY

Office of Environmental Health & Safety
718.270.1216

Controlled Substances in Research	
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I. Purpose

This document describes procedures that investigators must follow when storing or using controlled substances for purposes of researching controlled substances or in the administration of controlled substances as an experimental, anesthetic or analgesic agent in vertebrate or invertebrate animals.

II. Policy

Downstate is committed to complying with all regulations involving controlled substances including but not limited to the federal Code of Federal Regulations (Title 21, Chapter 2)[1] and state law or regulation (Title 10, Part 80)[2]. The U.S. Drug Enforcement Administration[3] (DEA) strictly regulates controlled substances and precursor chemicals. Due to their abuse potential, controlled substances are subject to licensing, registration, storage, security, use, and disposal requirements. In addition, the New York State Bureau of Narcotic Enforcement[4] provides oversight of state-controlled substance rules and regulations including licensing and diversion control. This policy applies to all employees, students, University affiliates and visitors.

III. Definitions

A. Principal Investigator: an individual who is granted the authority to lead and conduct a research project. They are responsible for the overall scientific and technical integrity of the project, ensuring compliance with regulations and ethical guidelines. Principal Investigators (PIs) using controlled substances and controlled items in their research (including human and animal research) must comply with applicable laws, regulations, and requirements. These requirements (including licensing/registration) are separate from, and in addition to, any that apply to medical practitioners. All investigators, including clinical practitioners, using controlled substances in research must obtain licensing/registration for use of controlled substances.

B. Authorized User: Refers to personnel designated by the Principal Investigator (DEA Registrant) to have access to controlled substances. This individual can be the lab supervisor or manager.

IV. Responsible Parties: Principal Investigators, Office of the IACUC, Environmental Health & Safety, Division of Comparative Medicine (DCM)

[1] https://www.ecfr.gov/current/title-21/chapter-II/part-1301?toc=1
[2] https://regs.health.ny.gov/volume-1a-title-10/content/part-80-rules-and-regulations-controlled-substances
[3] https://deadiversion.usdoj.gov/
[4] https://www.health.ny.gov/professionals/narcotic/

V. Procedures[5]

A. Requirements for Acquisition

1. The appropriate acquisition method varies depending upon how, where and which controlled substances are used. All acquisitions for animal use must be pharmaceutical grade products except where described in the IACUC protocol. Controlled Substances for use in research that does not require IACUC approval (i.e. *in vitro* or other) MUST be obtained by the PI directly from an outside commercial vendor or governmental agency. Such acquisition occurs under the auspices of the PI's controlled substances researcher registration.

    - Euthanasia products such as Euthasol® are not pharmaceutical grade, and the purpose is exclusively for euthanasia. This product may not be used for anesthesia. Note: this product is FDA-approved, while other similar pentobarbital sodium products are not FDA-approved.
    - Products labeled for research animal use only may not be pharmaceutical grade. Product package information inserts from chemical grade anesthetic suppliers may state that the product *produces rapid and reversible anesthesia in experimental animals*. Although this may be true, **pharmaceutical-grade** may only be **used** when the **pharmaceutical grade** is unavailable or when there is a **scientific justification.**

2. PIs must obtain their own state and federal controlled substance research licenses. For those that do not currently possess a DEA registration that wish to use controlled substances in research, a NYS Department of Health Bureau of Narcotics Enforcement (NYS DOH) controlled substance license must be obtained first. You MUST receive your NYS DOH license before applying for your DEA license. The DEA will not provide a federal license until the PI obtains a state license.

    Here are the steps for registration:

    - First, submit an **DOH-4330** application form for a **class 4 researcher license**, NOT practitioner, with the NYS DOH.
    - Once the NYS license is acquired, submit a DEA 225 form under **researcher**, NOT practitioner.

3. PIs may source controlled substances for use in IACUC-approved research in animals from an outside commercial vendor or governmental agency. Such acquisition occurs under the auspices of the PI's controlled substance researcher registration, and may require the use of a DEA Form. Refer to DEA and BNDD links below.
4. PIs may source controlled substances from the Division of Comparative Medicine for administration only by DCM staff, fee for service. Such acquisitions by the PI occur under the auspices of their own license unless an analgesic reviewed on a case by case basis.
5. PIs may source a DCM veterinarian only for Buprenorphine ER, a compounded analgesic, by veterinary prescription. Specific animal ID, body weight and species is required.
6. **An investigator or protocol personnel must administer controlled substances purchased on that investigator's license on animals housed under that same**

[5] Adapted from Controlled Substances, Washington University in Saint Louis, retrieved 5 April, 2024. https://research.wustl.edu/storage-security-guidelines/

investigator's IACUC protocol. For example, a technician who works for more than one investigator who is registered with the DEA, may only administer controlled substance to animals of the same PI (e.g., the owner of the controlled substance must match the owner of the animal).

7. Detailed instructions on obtaining DEA and DOH researcher registrations are available on the agencies' websites:

   - DEA: https://deadiversion.usdoj.gov/drugreg/registration.html
   - NYS Department of Health: https://www.health.ny.gov/forms/doh-4330.pdf

8. New York State controlled substances for any use in research must be obtained using a Class 4 license, a controlled substance research license, rather than a practitioner license.

9. **Once licenses are obtained and/or renewed, licenses must be submitted to the Office of Environmental Health and Safety.**

B. Training

1. PIs with DEA registrations are required to take the EH&S "Controlled Substances Management in Research" training **annually** to keep current on controlled substance requirements.

2. Training is administered on EH&S online training software. Reach out to the safety office at environmental.safety@downstate.edu for access to the course.

C. Institutional Animal Care and Use Committee (IACUC) Protocols

For animal research that use controlled substances, the PI must:

1. Provide information regarding the use of controlled substances in their IACUC protocol, (i.e., specific drugs, dose ranges and approximate volumes required to complete the objectives of the protocol);
2. Specify lab personnel who will have access to controlled substances; and
3. Ensure education is completed for authorized users.

D. Controlled Substance Record Retention

All Investigators are responsible for maintaining the following records documenting acquisition, use, and disposal of controlled substances and adhere to the corresponding record retention timeframes.

Inventory of Controlled Substances	Records of the biennial inventory of controlled substances on-hand	5 years after inventory date	21 CFR 1304	NYS retention period is 5yrs (Title 10 Part 80 Section 112 and 134)
DEA Form 222	Copies of Form 222 submitted for the purchase of Schedule I and II drugs including the invoice and packing slip	5 years from the date of transaction	21 CFR 1304	NYS retention period is 5yrs (Title 10 Part 80 Section 100)

Disposal/Destruction of Controlled Substances	Records of controlled substances sent for disposal/destruction	5 years after disposal	21 CFR 1305	NYS retention period is 5 years (Title 10 Part 80 Section 51 (d)

E. Controlled Substance Inventories (Initial and Annual)

1. **Controlled Substances Initial Inventory Form.** Upon first receipt on the day of arrival of each controlled substance, the investigator must have on file a paper Initial Inventory of the controlled substance. It is recommended the inventory records be maintained close to the secured storage location for ease of access and review during audits. Information on the Initial Inventory will include:
    - date of initial stocking of controlled substance
    - investigator name
    - storage location(s) where controlled substances are stored
    - names of authorized personnel performing the inventory
    - whether inventory was recorded at the beginning or end of the business day
    - drug name
    - drug strength (mg/ml, mg/tablet, %, etc.)
    - drug dosage form (bottle, tablets) and quantity in stock (number of full bottles, amount in a partial bottle, number tablets, etc.)
    - Schedule II drugs must be maintained on a separate form.

2. **Controlled Substances Biennial Inventory.** Biennial Inventory must be performed in a single workday every two years after the previous inventory. PIs must perform their biennial inventory within 30 days before previous one. (eg. Inventory taken **11/21/2024**, next inventory taken between **10/21/2025-11/21/2025**. The time of the inventory must be recorded (i.e. the amounts must be accurate as of the beginning of the workday or the end of the workday). Information is entered into the EH&S database, and the biennial inventory includes updated information on the bullet points outlined in the above initial inventory.

3. **Drug Use Log.** Drug use logs must be completed in full on the same day as use or administration.

F. Drug Storage

1. Investigators are to maintain drugs in a secure location as described the NYS Bureau of Narcotic Enforcement application. Substances shall be stored in a locked, substantially constructed cabinet (in accordance with 21 CFR §1301.75) except when they are in use. Substances must be returned to storage immediately after use. Confirmation of appropriate security measures are conducted during lab inspections.

2. All spills, evidence of theft or loss or inventory discrepancies must be reported to EH&S within 24 hours from initial discovery. This is reviewed on a case by case basis). Once reported and reviewed, EH&S advises the PI to complete the DEA Form 106— Theft or Loss of Controlled Substances and the NYS DOH Loss of Controlled substances Report Form 2094.

3. Storage in Safes

    a. Main Stock Safe.

i. The main stock safe requirement for schedule III-V is a securely locked cabinet of substantial construction with appropriate diversion measures in place, (e.g., within a locked office with limited access).
ii. Key control and safe access to main stock is limited to only registrant *and the* registered authorized user. When only two persons require controlled substance access, a working stock safe is not required.

b. Working Stock Safe.
i. The working stock safe requirement for schedule I-IV is a stationary, locked double cabinet: two doors each uniquely keyed. Both cabinets, inner and outer shall have key-locked doors with separate keys; spring locks or combination dial locks are not acceptable. For new construction, cabinets shall be made of steel or other approved metal.

ii. Key control and safe access to working stock is limited to registrant and employees for no more than 72 hours. When controlled substances **remain in the working stock storage for more than 72 hours, it is still working stock storage and is in violation of NYS BNE approved storage and increases potential for diversion.**

c. Keys to the safe must be stored in a securely locked cabinet of substantial construction where only ***the licensee and authorized user have access.*** Keys to storage areas must be accessible only to those authorized individuals. The key that locks the cabinet where Controlled Substances are stored must be locked up or may be kept on a person, who is an authorized user, or in some other secure manner to ensure non-authorized users do not have access to the controlled substances.

d. Non-controlled substances shall not be stored in the same safe as controlled substances.

e. Controlled Substances must be kept in their original containers (e.g. the same substance with different lot or expiration dates must not be combined.)

5. Controlled substances mixed with another drug (e.g., ketamine and xylazine) or diluted with sterile saline expire in 30 days after dilution or combination. Label secondary vessel with expiration date (Exp. DD-MM-YY). Inventory drug use logs for this aliquot must be created and maintained. If investigators combine stock bottles of controlled substances (e.g. ketamine) with other non-controlled drugs (e.g. xylazine or medetomidine) to make up “rodent cocktail” solutions, an appropriate entry must be recorded on the original stock bottle’s Controlled Substance Aliquot Log and a new, separate Controlled Substance Aliquot Log must be generated and maintained by the investigator to record activity associated with the compounded product.

6. As controlled substances are dispensed in the course of performing animal research, the date, species, animal ID (USDA covered species only), amounts used, drug balance remaining in bottle, and purpose of use are to be recorded on the Controlled Substance Aliquot Log and initialed by the authorized lab personnel. For non-covered species, the animal ID is the number of animals that were administered controlled substances on that day.

7. When the bottle is empty, disposal must be logged among the DEA registrants' records. Empty bottles of controlled substances must have the label removed or rendered unreadable prior to disposal. The empty bottle must be disposed of in a sharps container.

8. If any amount of controlled substance drawn from the bottle is not used in the animal, this excess amount is considered "contaminated by animal contact" and should be disposed (disposal procedures below) by the PI and the wastage noted in the Controlled Substance Aliquot Log.

9. In USDA-covered animal species with individual medical records, amounts of controlled substances administered must also be recorded in the medical record.

10. If an investigator obtains controlled substances from different controlled substance licenses, **the controlled substances must be stored in separate, secure storage units** to reflect the difference in the registrations used to obtain the controlled substances.

11. Prescription controlled substances schedule III-V shall be stored in main or working stock safe and may be stored in same storage unit (exempt from above requirement).

G. Disposal

1. The appropriate disposal method varies depending upon how the expired, contaminated or unwanted controlled substances were originally acquired. EH&S, DCM and University Pharmacy is not authorized to remove controlled substances from your individual registration. *Contact the Environmental Manager for your campus for assistance in determining proper disposal procedures that includes working with an authorized New York State Reverse Distributor.*

a. Reverse Distribution. The DEA defines reverse distribution to mean the acquisition of "controlled substances from another registrant or law enforcement for the purpose of: (1) return to the registered manufacturer or another registrant authorized by the manufacturer to accept returns on the manufacturer's behalf; or (2) destruction." The U.S. Drug Enforcement Administration (DEA) requires any reverse distributor that engages in "reverse distribution" to hold a DEA registration.

A reverse distributor receives unwanted, unusable, or expired pharmaceuticals from a registrant that ships the product(s) directly to the reverse distributor. In these situations, the reverse distributor will either physically transport the pharmaceutical products itself or ship the products to its destruction facility via the U.S. Postal Service or common carrier. List of New York State independent reverse distributors:

https://www.health.ny.gov/professionals/narcotic/licensing_and_certification/docs/reverse_distributor.pdf

b. Chemical Destruction. Only Buprenorphine ER acquired by veterinary prescription may be disposed via chemical destruction (Rx Destroyer®). Please review "Disposal of Controlled Substances Using Rx Destroyer" document for Rx

destroyer use instructions. Rx Destroyer Usage Procedure can be reviewed in appendix A of this document, or on the EH&S Downstate webpage.

2. Disposal Deadline. Expired controlled substances shall be disposed once annually. If disposal of expired substances cannot be disposed of annually, reach out to EH&S for allowances or assistance with disposal.

H. Audits

Both the Institutional Animal Care and Use Committee and Environmental Health and Safety audits the investigator labs at least annually. IACUC staff visits each lab to review all aspects of animal care and use identified on the IACUC protocol. Among the items checked on these visits will include, but may not be limited to: the list of authorized controlled substances users and completion of background checks, proper security of controlled substances, controlled substance use (aliquot) logs, controlled substance inventories, verification of lab personnel who have access to controlled substances and expiration status of controlled substances. EH&S reviews include but may not be limited to verifying proper security of controlled substances and completion of use logs and inventories. Individual registrations may be subject to external reviews.

I. Sanctions

Any lab found to be deficient in any aspect receives formal communications from the IACUC and/or Environmental Health and Safety office regarding the deficiency and the method for correction. Any lab with deficiencies is re-inspected to determine compliance. Violations of the policy, procedures, or regulations that are deemed serious or continuing may subject the covered individual to corrective actions or other sanctions as deemed appropriate by Institutional Officer, in consultation with the relevant department chair or dean. Non-compliance can warrant heavy fines or criminal charges issued by the DEA.

Appendix A

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Disposal of Controlled Substances Using Rx Destroyer

How does Rx Destroyer work?

Rx Destroyer contains a non-toxic, charcoal slurry that denatures medication rendering it irretrievable and safe from diversion.

Procedure to dispose of waste considered to be recoverable, e.g. unused doses, spillage, expired material via Rx Destroyer

1. To discard DEA controlled substances, a witness must be present.

2. Add material to bottle and tightly close the cap.

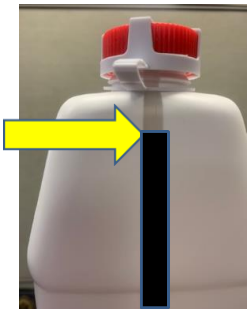
    - To Open Rx Destroyer: Push down and counter-clockwise to open red cap. Cap or lidded funnel should be closed between uses.

3. Record the waste amount on the usage log in addition to **DEA Form 41**. The witness will need to initial the log and sign the DEA Form 41. This record must be kept for **two years** along with the associated controlled substance records.

4. Gently shake bottle to mix

5. Store disposal container securely in the same registered location until ready for disposal.

6. Continue to add waste as necessary until contents are within 2 inches from the cap **OR** at one year from initial opening of the Rx Destroyer. **<u>The expiration date for an opened bottle of Rx Destroyer is one year from the open date.</u>**



7. For disposal, contact the Office of Environmental Health & Safety at x5212 or x1216