Penn’s Institutional Animal Care and Use Committee (IACUC) has adopted the following policy to define the responsibilities of the institution, facilities, and the Principal Investigator (PI) conducting animal research, teaching, or testing that uses controlled substances. Controlled substances are often used as the agent of investigation or for the provision of anesthesia, analgesia, sedation or euthanasia necessary for procedures to be performed without pain or distress. In animal research, teaching, or testing, research staff may only use controlled substances under an approved IACUC protocol that includes provisions for the use of the specific controlled substances. ULAR maintains its own inventory for use in clinical cases and post-operative animals.

The Drug Enforcement Agency (DEA) administers the Controlled Substances Act (CSA). Non-compliance with the CSA may result in “personal” fines to the registrant, and neither grant funds nor institutional funds are permitted to be used for payment. All controlled substances are assigned into one of five “schedules” designated by the DEA, but very few are commonly used for veterinary care in an animal research setting. A complete list of all controlled substances may be found on the DEA website. Common controlled drugs used in animal research such as sedatives, anesthetics, or analgesics include, but are not limited to:

- Opioids - fentanyl, buprenorphine, hydro-/oxymorphone, butorphanol
- Dissociatives – ketamine, tiletamine (Telazol)
- Benzodiazepines – midazolam, diazepam, zolazepam (Telazol)
- Barbiturates – pentobarbital, thiopental, euthanasia drugs (Euthasol)

Compliance with this policy is required of any PI or research staff member using any controlled drug in animal research. The Vice Provost for Research has determined that awareness and compliance with this policy will be confirmed during normal IACUC semiannual inspections and post-approval monitoring visits by compliance liaisons. This policy provides guidance to the research community with information about how to manage controlled drugs—from registration to disposal.

- Registration
- Modification of an Approved Registration
- Security and Storage
- Acquiring Controlled Drugs
- Record-keeping
- Authorized User List
- Theft of Controlled Drugs
- Disposal of Expired, Unwanted, or Unneeded Controlled Drugs

MANAGING CONTROLLED SUBSTANCES REQUIRES CONSTANT ATTENTION
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REGISTRATION

Each principal investigator (DEA registrant) conducting animal research using DEA controlled substances will be responsible for registering with the DEA and for assuring compliance with applicable state and federal regulations. As an alternative, a PI may list anyone who has a DEA registration on their protocol as a co-PI in order to obtain and use controlled substances. A justifiable explanation of how this individual is involved in the laboratory’s work and the consent of the registrant must be available. The registrant may not allow their registration to lapse until all controlled substances are spent, disposed of, or transferred to another registered person. Best practice is to have the PI, or at least the co-PI, of the protocol be the DEA registrant as well as be responsible for maintaining the controlled substance inventory.

If there is no one available with a DEA registration that can be listed as a PI or co-PI on the protocol then it is acceptable to list the departmental DEA registration typically held by the department chair. This practice is highly discouraged because the registrant is responsible for maintaining adequate supervision of the use, storage, and disposal of all controlled substance purchased with their registration, including supervision of all personnel (research and laboratory staff) authorized to use such compounds in animal research. Failure to adhere to regulations may result in substantial personal fines to the registrant from the US Drug Enforcement Agency.

Licensed medical doctors and veterinarians may use their practitioner registrations to acquire controlled drugs for research purposes. Separate registration may not be required for practitioners who are already registered and engaging in research with controlled substances in schedules II, III, IV, or V (CSA, section 823. Registration Requirements (f)). Schedule I includes “non-medicinal” drugs not typically covered with a practitioner registration, thus use of these drugs will likely require a separate research registration. Non-medical professionals (e.g., PhD scientists) may register with the DEA and obtain a research registration in order to use specific drugs related to the research project.

- Practitioner registrations must be renewed every three years and use Form 224 (initial registration) and 224A (renewal).
- Professionals acquiring a separate research DEA registration for research purposes should complete the online application or DEA Form 225.
- Research DEA registrations must be renewed annually. Renewals may be completed online using Form 225A. Federal research funds may not be used to pay registration fees.
- A research registration includes only the specific controlled drugs to be used on the IACUC protocols. Be sure the application includes all controlled drugs listed on all protocols for which the registration is the PI or Co-PI.
- The certificate of registration (Form 223) must be maintained at the registered location and kept available for official inspections.
- If a research registrant has more than one location (defined as separate street addresses) where controlled substances are maintained, administered, and/or dispensed, then a separate registration is required for each location.

Medical doctors and veterinarians using their practitioner registrations for research purposes are exempted from state registration requirements as described in the Pennsylvania Controlled Substances, Drugs, Device, and Cosmetic Act. At this time, researchers are not required to obtain a Pennsylvania controlled substances registration. A Pennsylvania specific registration is not required as long as the research is approved by a scientific institution/University and is within the scope of designated research.
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The only exception to this is the use of human chorionic gonadotropin as this agent is controlled by the state, but is not federally controlled. If your research uses HCG, you should contact the Philadelphia DEA office for further information about registering for this agent.

MODIFICATION OF AN APPROVED REGISTRATION

There are a number of common changes to a DEA registration that many people overlook. A modification of registration can be requested online or by writing to the local DEA Registration Program Specialist responsible for the region.

1. New drugs: Research registrations are approved for specific drugs. If you need to use a controlled substance that you do not currently have listed, then you must amend the registration to add this new drug.

2. Change of address: The address on the registration is the physical address of the storage location of the controlled substances. If the laboratory relocates and the controlled substance will be stored in a new physical location, approval by the DEA is required. If the change of address involves a change in the state, the proper state issued license and, if applicable, state controlled substances registration must be obtained prior to the request to the DEA for an address change. If the modification is approved, the DEA will issue a new certificate of registration. The registrant should maintain the new certificate with the old certificate until expiration.

SECURITY AND STORAGE

Registrants “are required to store stocks of Schedule II through V controlled substances in a securely locked, substantially constructed cabinet” ([DEA Practitioner’s Manual](https://www.deadiversion.usdoj.gov/regulations)) with limited access.

- The “container” may be a secure cabinet, drawer, safe, or lockbox affixed to a permanent structure. A container that is not bolted to a permanent fixture and simply kept in a drawer is not acceptable unless prior approval from the DEA has been obtained.
- When securing a lockbox to a permanent fixture, carriage bolts should be used so that they cannot be removed. The nuts should be within the lockbox, i.e. the nuts and bolts that could be removed to move the lockbox should be inaccessible.
- Visibility and accessibility of the container to the casual laboratory visitor should be prevented by placing it in a room with a lockable door.
- Some controlled substances may require refrigeration (e.g., Sustained Release Buprenorphine, Telazol, Dronabinol, etc.), necessitating storage in a locked box secured (e.g., bolted) to the inner wall of a refrigerator.
- After the required amount of drug to be administered is retrieved from the primary vessel (vial, box, syringe), the primary vessel shall be promptly returned to the locked container. The required amount of drug obtained from the primary vessel should be administered as soon as possible after acquisition.
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- The key or combination to the “container” should be different from the key to the office or room where the drugs are stored and should be available only to the registrant and authorized users listed on the authorized users list.
- Alternatively, a building or enclosure within a building which has been inspected and approved by the DEA or its predecessor agency, BND, and continues to provide adequate security against the diversion of Schedule III through V controlled substances, of which fact written acknowledgment has been made by the Special Agent in Charge of DEA for the area in which the building or enclosure is situated may be appropriate. It is best practice to still store Schedule III through V substances in a lockable container such as a safe which is held inside another lockable storage area.
- Schedule I agents have more stringent security requirements and must be maintained in a securely locked and substantially constructed cabinet. A strong metal cabinet or heavy safe fastened to a permanent structure is typically adequate.
- Blank DEA Form 222 must also be securely stored. This form should be maintained separately from the general log records.
- In order to better assure compliance and prevent diversion, it is strongly recommended that registrants conduct routine (e.g. monthly, quarterly) audits of controlled drug inventories.

Minimally, a biennial inventory audit must be conducted and documented for practitioner and research registrants (DEA Practitioner’s Manual). It is recommended that inventory be conducted on a more regular basis such as quarterly. A sample inventory form is available for download and use for tracking inventory assessments. Failure to generate required reports/audits may result in penalties (CSA, section 842. Prohibited acts B (c)(1)(A-B)).

ACQUIRING CONTROLLED DRUGS

Licensed practitioners and researchers may purchase controlled substances from the institution’s pharmacies. Pharmacies generally have required triplicate order forms. Purchase or transfer of schedule I & II drugs requires the use of DEA Form 222. Form 222 must be requested online by the registrant from the DEA and provided to the vendor at the time of order (copies 1 and 2 with attached carbon). The registrant, or their designee documented with a legal power of attorney, must sign Form 222 when ordering schedule II controlled drugs. The registrant must retain copy 3 of Form 222 with their records. The copy of form 222 must be maintained separately from other records and should be available upon inspection.

<table>
<thead>
<tr>
<th>All Penn researchers:</th>
<th>Researchers at SVM only:</th>
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</thead>
<tbody>
<tr>
<td>HUP Pharmacy</td>
<td>VHUP Pharmacy 215-898-7881</td>
</tr>
<tr>
<td>B-100 Silverstein</td>
<td>NBC Pharmacy  610-925-6196</td>
</tr>
<tr>
<td>215-662-2909</td>
<td></td>
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</tbody>
</table>

Alternatively, controlled drugs may be purchased from one of Penn’s preferred vendors. Because access to Penn’s online purchasing system is restricted, the department’s business administrator may need to submit any orders.

1. Login to BEN Financials.
2. Navigate to “Requisitioner”, then “Shop at Penn Marketplace”.
3. Consider a keyword search to narrow the list of vendors (e.g., “drugs”, “veterinary”).

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MANAGEMENT OF CONTROLLED SUBSTANCES

When acquiring controlled drugs, pharmacies require proof of DEA registration prior to their distribution. Acquiring Schedule I and II drugs generally requires DEA Form 222 to be submitted to the pharmacies (retain your copy of this form for your records). Additionally, certain vendors may require an exemption to needing a state registration. If this is needed, please contact the Pennsylvania Department of Health Drug, Device, and Cosmetic Program at 717-787-4779.

RECORD-KEEPING

Registered individuals are required to keep records, as described in the Controlled Substance Act. All records of drugs used on a research protocol “shall be kept and be available, for at least two years, for inspection…” (CSA, section 827. Records and reports of registrants (b)(3)). The DEA registrant is responsible for assuring that every authorized user documents accurate and timely records. It is recommended that all records documenting authorized users, purchasing, ordering, receipt (e.g. packing slips, Form 222 completed by pharmacies), dispensing, and disposal be maintained in one location in an organized manner for easy review and verification of use. Samples forms for all required documentation are available for download as an Excel file, with a separate tab for each type of form. Researchers are encouraged to download the file, review the documents, and use them for accurate controlled substance purchase, use, and disposal. Please contact the Office of Animal Welfare if you have any questions about how to organize your records or which documents are required to be maintained.

- All controlled substance records are subject to inspection by the IACUC as part of routine inspections related to evaluating the animal program.
- For schedules II-V, day-to-day usage records should be kept in logbook with all entries written in pen. Electronic records may be used if there is a mechanism to track entries and certify modifications to entries. Schedule I records must be maintained in a bound notebook with all pages intact. All order forms, packing slips, or pharmacy receipts/memos must also be maintained for at least two years (CSA, section 828 Order forms (c)(1)). They may be discarded after the biennial inventory is documented. Information that should be recorded in the logbook, immediately when inventory is received:
  1. Date received
  2. Name of medication
  3. Formulation (e.g. tablets, injectable, patch)
  4. Number of units (e.g. tablets, ml)
  5. Lot number
  6. Individually identified bottle (or other container)
  7. Expiration date
  8. Each unit/bottle/patch should be given an individual number so as to be easily tracked
  9. Initials by individual receiving/documenting receipt of the drug

- Information recorded when drugs are used should include at least:
  1. Date of withdrawal of drug from bottle/vial
  2. Animal ID number (USDA species)
  3. Amount withdrawn from bottle/vial (ml or tablets)
  4. Amount remaining in the container
  5. Authorized user’s initials
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6. Additional information **may** include the protocol number, cage card number, and the reason for use.

When a controlled substance is mixed with another agent (e.g., dilution of a drug with saline for accurate dosing, combination of compatible anesthetic agents) the new container should clearly state what substances are contained within and the concentration of the “cocktail”. The cocktail container should be labeled with its own unique ID and have a separate log sheet to track its use (administration, waste, etc.) similar to all other log sheets for single agents. All record keeping that has been described must be performed for any controlled substance that is mixed with another agent. Cocktails are to be maintained for no more than 30 days after compounding (see the IACUC policy “Expired Drugs and Materials”).

AUTHORIZED USER LIST

A list of **authorized users**, signed by the registrant, should be available for review. This list should be updated when new authorized users are added and current authorized users depart. Individuals on this list are the only personnel who may dispense or administer controlled drugs purchased and maintained by the registrant. The authorized user list must be readily available as the DEA will review this list upon a site inspection.

DIVERSION OF CONTROLLED DRUGS

**Theft or loss of controlled substances (diversion)** must be promptly reported to the DEA, Penn Police (215-573-3333), and the Office of Animal Welfare so that we can help you through the process. The report to the DEA should be submitted by **Form 106**. Failure to report theft or loss of controlled substances may result in penalties (CSA, section 842. Prohibited acts B (c)(1)(A-B)).

DISPOSAL OF EXPIRED, UNWANTED OR UNNEEDED CONTROLLED DRUGS

Expired, unwanted, or unneeded controlled drugs must be accounted for and disposed of in accordance with applicable State and Federal regulations (21 CFR Title 1317 Subpart A and Subpart C).

Expired controlled drugs must be clearly labeled as expired (e.g., “expired – do not use”) and kept in a separate place from non-expired drugs within the securely locked cabinet until they can be disposed of properly. Drugs (DEA-controlled or not) may NOT be used in animals if they are expired, per USDA Policy. Please see IACUC policy “Expired Drugs and Materials” for additional guidance.

Expired, unwanted, or unneeded controlled drugs may be disposed by any of the following options:

1. **Send drugs to a Reverse Distributor.** Please refer to this list of reverse distributors. Various distributors may have different specific procedures, so contact the distributors for specific instructions. The reverse distributor is responsible for submitting Form 41 or Form 222, as necessary, with the DEA.

2. **Relinquish the drugs to the HUP Pharmacy.** The HUP Pharmacy will only accept schedule II-V unopened controlled substances in their original containers. Prepare the **Drug Transfer Form** available on the EHRS website in advance - the HUP Pharmacy may not generate receipts. The
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HUP Pharmacy will complete Form 222 for schedule II substances relinquished to them. You must retain a copy of this with your records for a minimum of 2 years.

You should keep records of all substances that are relinquished to the HUP pharmacy or reverse distributors. The record should list the drug name, dosage form, strength, quantity, and date transferred.

For further information please contact:
U.S. Drug Enforcement Administration
Philadelphia Division
William J. Green Federal Building
600 Arch Street, Room 10224
Philadelphia, PA 19106
(215) 861-3474
http://www.justice.gov/dea/divisions/contacts/phi_contact.shtml