

Yale University

**Policy on the Use of
Controlled Substances in Research**

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Prepared for the University Safety Committee

by the

Offices of the Vice President and General Counsel and
Environmental Health & Safety

Additional Copies Available from
the Office of Environmental Health & Safety
(www.yale.edu/ehs)

Yale University
POLICY ON THE USE OF
CONTROLLED SUBSTANCES IN RESEARCH

1. Introduction

Due to their abuse potential, drugs identified by the US Department of Justice, Drug Enforcement Administration (DEA) or the Connecticut Department of Consumer Protection, Drug Control Division (DCD) as controlled substances are subject to extensive licensing, registration, storage, security, use, and disposal requirements. At Yale University, the Office of Environmental Health and Safety (EHS) has the responsibility for assisting researchers negotiate these requirements, including obtaining appropriate regulatory documents; EHS officials can be contacted at 785-3550 during regular business hours. Please note that this policy applies exclusively to the research use of controlled substances, including human subject studies. Medical practitioners are directed to consult their site of practice to review credentialing and controlled substances prescription privileges.

2. “Controlled Substance” Defined

Controlled substances are any “...drug, substance, or immediate precursor in schedules I to V, inclusive, of the Connecticut controlled substance scheduling regulations adopted pursuant to section 21a-243.”

3. Applicability

Principal Investigators (PIs) using controlled substances in their research (including research involving animals and non-therapeutic research involving human subjects) are subject to extensive state and federal regulatory requirements, as outlined in this Policy. Note that these requirements (including licensing/registration with regulatory agencies) are separate from and in addition to requirements that apply to medical practice; therefore MDs and MD/PhDs conducting laboratory or non-therapeutic human subject research involving controlled substances must obtain licensure/registration for laboratory use of controlled substances in addition to licensure for their practice. Please further note that therapeutic research, in which the subjects are receiving controlled substance(s) as part of their treatment, requires only the medical practice license, and not a laboratory research license. (The inclusion of subjects receiving only a placebo does not invalidate this exception.)

4. Schedules

Controlled substances are divided into five categories, known as Schedules. Schedules I and II are the most stringently regulated, and both have high potential for abuse. However, Schedule II drugs have a currently accepted medical use in treatment, while those in Schedule I do not. Schedule III drugs include many stimulants and depressants, pain-killers and cough suppressants, the veterinary anesthetic ketamine, and anabolic steroids. Schedule IV substances cover the balance of lower abuse potential stimulants and depressants, and Schedule V includes therapeutic drug mixtures containing very limited quantities of controlled substances.

Researchers planning work with controlled substances must be aware of and are responsible for complying with relevant state and federal statutes and regulations for these materials. The state and federal schedules of controlled substances are substantially similar, but not identical.

5. Licensing and Registration

Since the University cannot, by law, maintain “blanket” registration for controlled substances, it is the responsibility of individual Principal Investigators (PI) to obtain appropriate licenses and registration, and to adhere to applicable state and federal regulatory requirements when working with controlled substances. PIs must obtain research licensure from the CT DCD as well as registration from the federal DEA. A table summarizing the license and registration obligations by different research activities appears in Attachment A. Instructions for completing licensing/registration applications are summarized below:

A. State Licensing: PIs must complete both the Yale EHS “PTAEO Approval for State DCD Controlled Substance License” form and the State of Connecticut “Application for Controlled Substance Laboratory License”, and submit them (with charging instructions and business office authorizing signature) to Yale EHS for processing. As part of the application process, the DCD will inspect the designated laboratory work area; a copy of the DCD inspection checklist is attached to facilitate PIs review the items covered in their laboratory work areas to ensure that facilities and operations are consistent with DCD requirements. Approved applicants will receive a one-year license to work with controlled substances in a manner consistent with the approved use(s) described in the application. The DCD also conducts periodic random inspections of licensees thereafter.

B. Federal Registration: After receiving state DCD licenses from EHS, PIs will be provided with a research laboratory registration (Form DEA-225), along with another charging instructions request for the DEA license fee. These forms should be completed and returned to Yale EHS, where they will be processed for submission and payment to DEA. Note that for work with Schedule I substances, three copies of the research protocol must accompany the application form. Due to internal DEA protocols, PIs will receive their registration certificate (known as Form DEA-223) directly from DEA. Upon receipt of certificates, PIs should make a copy and forward it to Yale EHS. DEA registrations remain active for a 3-year period, at which time a renewal notice will be mailed to the PI. DEA has also implemented an on-line registration system that can be directly accessed upon successful state licensing.

C. Renewals: Notices of pending license and registration renewals will be sent out by Yale EHS several weeks prior to expiration. Renewals will be processed in the same manner as initial licenses.

Registrants seeking to modify, transfer, or terminate their research laboratory use license and/or registration must submit a written request to Yale EHS for processing with the regulatory agencies.

6. Purchasing Controlled Substances

Controlled substances are considered “restricted purchase items” at Yale University and may only be ordered through the Purchasing Department or, in the case of certain licensed operations (e.g., pharmacy), the Purchasing Department’s approved designee. Researchers are required to

provide a copy of their current license to the Purchasing Department at the time of each purchase. PIs involved in human subjects research must obtain their controlled substances by prescription from an approved Investigational Drug Service or research pharmacy. Please note that Medical Practitioners may NOT use their prescription privileges to order controlled substances for *in vitro* benchtop or *in vivo* animal laboratory research.

7. Scope of Use

Controlled substances may be used only for duly authorized, legitimate medical or scientific research purposes, to the extent permitted by a registrant's license and registration, and in conformity with state and federal statutes and regulations.¹

8. Storage and Security Controls

Controlled substances must be maintained in a manner and location that comply with state and federal law. Any controlled substances not so maintained are subject to seizure by and forfeiture to the state. Failure to comply with applicable requirements may also result in a suspension of the PI's purchasing privileges and disciplinary actions through the University Safety Committee.

In order to guard against theft or diversion, all controlled substances - regardless of schedule - must be kept under lock and key, and accessible only to authorized personnel. The number of authorized staff must be kept to the minimum essential for efficient operation, and the stocks of controlled substances must be limited to the smallest quantity needed.

Security requirements vary by drug schedule. Schedule I and II controlled substances are subject to the highest security requirements, and must be stored separately from other drugs in an approved safe (as defined below). Schedule III through V substances must also be stored separately from other drugs in a secure locked location. Regardless of schedule, all controlled substances must be kept locked in their storage location except for the actual time required for authorized staff to remove, legitimately work with, and replace them.

Safes for Schedules I and II:

An approved safe is one approved by the DCD or DEA prior to January 1, 1975, or any safe that minimally conforms to *all* of the following standards:

- a. Safe Manufacturer's National Association certified as being Class A, B or C.
- b. Underwriters Laboratories certified as being inspected for one or two hours.
- c. Underwriters Laboratories certified as being equipped with a relocking device.
- d. Weight of 750 pounds or more, or rendered immobile by being securely anchored to a permanent structure of the building.

EHS can provide recommendations for safes that comply with these requirements.

¹ Pursuant to the Drug-Free Workplace Act of 1988, Yale University prohibits the unlawful manufacture, distribution, dispensation, possession, or use of any controlled substance at the workplace. In addition, the University prohibits the unlawful possession, use, or distribution of illicit drugs and alcohol by faculty, staff, and students on its property or as part of any of its activities in accordance with the Drug-Free Schools and Communities Act Amendments of 1989. Violation of these Yale policies can lead to disciplinary action, up to and including termination.

9. Export

Federal law prohibits the export of controlled substances unless certain requirements are met, including, in most cases, export and import permits. Violators of the law risk arrest at U.S. Customs or on airplanes, imprisonment, and fines both in the United States and foreign countries. Licensed brokers are available for transport of controlled substances. Yale EHS can provide assistance in arranging for any necessary transport of controlled substances.

10. Authorized Staff

PIs may authorize members of their laboratory staffs to work with controlled substances under their license/registration, provided staff members have been listed on the license and registration applications. In the case of non-therapeutic human subject research, authorized staff must also be appropriately credentialed to administer such materials to patients. Authorized staff must follow all of the rules and regulations outlined and referenced in this Policy, and are also obliged by law to immediately report any loss or diversion of controlled substances to their PI, Yale Police Department, and Yale EHS. Persons previously convicted of a felony offense relating to controlled substances or who, at any time, had an application for registration with the DEA denied, had a DEA registration revoked, or surrendered a DEA registration for “cause”, may not be authorized for work with these materials. (In this instance, “cause” is the surrender of a license or registration resulting from a federal or state investigation into an individual’s handling of controlled substances.)

11. Recordkeeping

PIs must maintain complete and accurate inventory records for all controlled substances. These records must be kept separately from all other records and documents, in or near the primary work area, and be readily available for inspection during regular work hours or at any other reasonable time. Records must be written, typewritten, or printed form. The use of codes, symbols, or foreign languages in identifying a controlled substance or person in the record is prohibited. Records should be kept in such a manner as to facilitate quick and accurate assessment of quantity on hand and history of use to the individual container level. In the event that any controlled substances are lost, destroyed, or stolen, the kind and quantity of the material and the date of discovery of such loss must be recorded in detail. All records must be maintained by PIs for a period of at least three years from the date of the last recorded purchase, transfer, use, or other transaction involving the controlled substance.

The recordkeeping system must include *at least* the following information maintained as prescribed in state and federal controlled substance laws and regulations:

A. Receipt of Controlled Substance: A separate and current record of the receipt of controlled substances, indicating date received, name and address of supplier, and the type, strength or concentration, and amount of the controlled substances received. Each record must be signed by the person receiving the controlled substance. DEA Forms 222 and invoices should be maintained as applicable.

B. Use of Controlled Substances: A separate and current record for the storage and use of each controlled substance (use meaning to administer, dispense, professionally use, or otherwise dispose of), indicating the date, building and room, specific research

experiment, controlled substance's application in the research, and type, strength and quantity of each controlled substance use. The record must also include the name and address of the person to whom, or for whose use, or the owner and species of animal for which, the substances were administered or dispensed. By noting starting volume or mass of substance in the container, each use is a subtraction from the starting quantity, and the running (decreasing) amount should equal the total amount remaining on-hand. Each record of use must be signed by the person working with the controlled substance. The inventory should also include a detailed list of any controlled substances lost, destroyed, or stolen, including the type, strength, and quantity of such substances, and the date of the discovery of such loss, destruction, or theft. See Section 13 for more information.

C. Biennial Inventory of Controlled Substances: A complete and accurate inventory of the stock of controlled substances within each PI's laboratory must be recorded when he/she first engages in research with controlled substances and then biennially thereafter, within four days of May 1 of each *odd numbered year* (2009, 2011, 2013, etc.). The inventory can be taken either as of the opening of business or the close of business on the inventory date and this should also be noted on the inventory. The type, strength, and quantity of all controlled substances must be recorded at this time in the manner prescribed in DEA regulations. The person conducting the inventory must also date and sign the record. Reminder notices and forms will be distributed by Yale EHS several weeks in advance. This biennial inventory must be retained on the laboratory premises for three years, separate from other business records and readily available for potential regulatory review as described above.

12. Disposal

Controlled substances from non-human research work may only be disposed under witness from the State DCD or Federal DEA, through a reverse distributor by documented return to the supplier or manufacturer, or as otherwise authorized or directed by regulatory agency personnel. Expired material, unused or unwanted product, or neat waste must be accumulated and stored under lock and key until ready for disposal. The State DCD, Federal DEA, or Yale EHS should be contacted to arrange for a disposal visit or permission to otherwise dispose of controlled substances. Controlled substances injected into research animals, consumed in a reaction, or converted into a non-recoverable hazardous waste mixture may be disposed of through routine waste disposal procedures available from Yale EHS and the Yale Animal Resources Center. Unused or unwanted controlled substances derived from human subject research must be returned to the Investigational Drug Service for disposal, or locally disposed to sewer upon double-witness by authorized research staff.

13. Reporting of Loss, Destruction, Theft, or Unauthorized Use

Any losses of any controlled substance, including thefts, unauthorized uses, or unauthorized destruction must be reported to the Yale Police Department and Yale EHS immediately upon discovery. Registrants must also document the incident in writing for submittal to the State DCD (within 72 hours) and Federal DEA (within one business day). The written statement must describe the kinds and quantities of controlled substances in question, and the specific circumstances involved. If the circumstances are unknown, immediate notice should still be

given to regulators and a complete statement provided thereafter if the loss is substantiated. Regulators should be kept apprised of any ongoing investigation and notified if the loss is not subsequently substantiated. In addition, where a controlled substance is stolen, lost, or destroyed in transit, the consignee (and consignor if within this state) is also required to prepare a loss report that includes documentary evidence that local authorities were notified. The registrant should retain a copy of the statement for at least three years.

14. Resources and References

Department or Agency	Phone	FAX
Yale University Purchasing Department 155 Whitney Avenue	432-9955	432-9966
Yale Office of Environmental Health & Safety 135 College Street (www.yale.edu/ehs)	785-3550	785-7588
Yale University Police Department	911 (any Yale phone) 432-4400	432-4416
CT Drug Control Division (DCD) 165 Capitol Ave Hartford, CT 06106 (www.ct.gov/dcp)	860-713-6065	860-713-7242
US Dept. of Justice, Drug Enforcement Division (DEA) (www.dea.gov)	860-240-3700 (Hartford Area Office)	860-240-2658 (Hartford Area Office)

Copies of this Policy and all attachments are available from Yale EHS at www.yale.edu/ehs. Copies of current drug schedules and state polices are available from the CT Drug Control Division by mail or web site (www.ct.gov/dcp).

15. Attachments

- A. Categories for Licensing Use of Controlled Substances in Research
- B. Yale University Office of Environmental Health & Safety “PTAEO Approval for State DCD Controlled Substance License”
- C. CT Drug Control Division “Application for Controlled Substance Laboratory License”
- D. CT Drug Control Division Laboratory Inspection Checklist
- E. “Drug Receipt Record” Form (Sample)
- F. “Controlled Substance Use” Form (Sample)
- G. “Biennial Controlled Substance Inventory” (Sample)

Attachment A. Categories for Licensing Use of Controlled Substances in Research

Elements	Laboratory Research (Animal or <i>In Vitro</i> Experiments)	Human Subjects	
		Therapeutic Use	Non-Therapeutic Use
Drug Licensing & Registration Expectation	Laboratory Researcher License (CT) plus Researcher Registration (DEA) (CGS 21a-246)	Medical Practitioner (CGS 21a-317)	Medical Practitioner plus: <ul style="list-style-type: none"> • Researcher Registration (DEA) • Laboratory Researcher (CT) (CGS 21a-246 and -317)
General Use Examples	Controlled substances used for anesthesia, pain management, or research in laboratory animals pursuant to IACUC approval or <i>in vitro</i> work. Subject to EHS review	Controlled substances used for intended therapeutic applications	Controlled substances used for basic imaging, observation, behavioral, or biochemical studies, or other non-therapeutic purposes
Typical Use Settings	Traditional “wet lab” settings	Clinical/clinical support and service settings, including various imaging facilities	Same as Therapeutic
Responsible Parties	Administration by or under direct supervision of a PhD, DVM, or appropriately trained MD	Administration by MD or appropriately licensed healthcare professional under direction of MD pursuant to IRB-approved protocol. MD retains on-going responsibility for patient care.	Same as Therapeutic
Management of Controlled Substance(s)	Researcher is responsible for ordering, purchasing, storage, and inventory	Procured and administered by prescription only, typically through third-party Investigational Drug Service (IDS) (“research pharmacy”)	Same as Therapeutic
Preparation of Controlled Substances	Typically procured in bulk quantities, requiring mixing or dilution prior to use	Patient-specific unit doses only prepared by registered pharmacist. May or may not be the active compound depending	Same as Therapeutic

Elements	Laboratory Research (Animal or <i>In Vitro</i> Experiments)	Human Subjects	
		Therapeutic Use	Non-Therapeutic Use
		upon protocol and/or blinding	
Recordkeeping	Licensed laboratory researcher maintains all records	Purchasing, inventory, and disposal records by registered pharmacist; proof-of-use sheets and patient blinding provided by pharmacy; MD completes proof-of-use sheets	Same as Therapeutic
Disposal	Unused/waste material maintained by researcher in laboratory until witnessed disposal by DCD	Unused/waste material returned to pharmacy. Partial unused doses may be locally disposed upon double-witnessing by MDs or RNs	Same as Therapeutic
Storage and Use Locations	Consistent and inspectable drug storage and use locations	Authorized pharmacy is drug origin and storage location; use locations may vary depending upon clinical testing or imaging site. Secure on-site standard storage needed for any material not under personal control of MD.	Same as Therapeutic, plus storage location must be inspected as part of Laboratory Researcher license application.
Additional Institutional Oversight Mechanisms	IACUC protocol reviews and approvals for all animal studies; EHS Safety Advisors, PI registration, laboratory inspections, and safety committees as applicable	Enrolled as patient with assigned Medical Record Number (MRN); GCRC reviews as applicable to study type and funding agency; HIC/IRB reviews and approval	Same as Therapeutic