Attaining Proper DEA Licensing and Maintenance of Controlled Substances in Researcher Laboratories

Much of this material was taken from the EHS Laboratory Safety Manual, Chapter 9

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Summary for acquiring a license
You must hold both a state (DHHS) and federal (DEA) registration
State license is acquired prior to a federal license
It takes about 3 months to complete the state license procedure
It takes about 2 more weeks to complete the federal license procedure
State licenses require on-site inspections
Each PI should obtain his/her own license, with drugs from approved IACUC protocols listed
You must know which schedule(s) your controlled substances are in
A state licensing fee is required with submission of license request
The fee cannot come from federal grant funds- use departmental, non-federal, or personal funds
Annual renewals for the state license are due in October
Annual renewals for the federal license are due on the anniversary of the initial approval
Introduction
Because of their potential for abuse, controlled substances have specific regulatory requirements for their acquisition, storage, security, use, and disposal. **Controlled substances** are any drugs or chemical substances whose possession and use are regulated under the United States Controlled Substances Act, or the North Carolina Controlled Substances Act. The U.S. Department of Justice, Drug Enforcement Administration (DEA) administers the federal law, and the North Carolina Department of Health and Human Services (DHHS), Drug Control Unit administers the state law. Controlled substances have stimulant, depressant, or hallucinogenic effects on the higher functions of the central nervous system, and tend to promote abuse or physiological/psychological dependence.

Schedules
Substances regulated under the U.S. Controlled Substances Act (CSA) are in one of five schedules. Schedule I substances have the most restrictions, and Schedule V substances the least. The CSA defines the schedules as follows:

Schedule I: Drug or other substance with a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety protocols for use under medical supervision.

Schedule II: High potential for abuse; a currently accepted use in treatment in the United States, or currently accepted medical use with severe restrictions; abuse may lead to severe psychological or physical dependence.

Schedule III: Potential for abuse less than Schedule I or II substances; currently accepted medical use in treatment in the United States; abuse may lead to moderate or low physical dependence or high psychological dependence.

Schedule IV: Low potential for abuse relative to Schedule III; currently accepted medical use in treatment in the United States; abuse may lead to limited physical or psychological dependence relative to Schedule III.

Schedule V: Low potential for abuse relative to Schedule IV; currently accepted medical use in treatment in the United States; abuse may lead to limited physical or psychological dependence relative to Schedule IV.

Appendix 9-A in the EHS Lab Safety Manual is an alphabetical list of the drugs and substances currently regulated by the CSA, and their corresponding schedule.

Registration and Acquiring a License
Only registered personnel with the appropriate state and federal licenses can order controlled substances. The controlled substance registrant must hold both North Carolina Department of Health & Human Services (DHHS) and federal Drug Enforcement Agency (DEA) registrations. To order controlled substances, you must register at the state level with the NC-DHHS, Drug Control Unit and the Federal level with the DEA.

In North Carolina, individuals must obtain the state controlled substance registration prior to applying for a federal controlled substance registration.

Each principle investigator (PI) should obtain his/her own Controlled Substance registration. DHHS will allow a departmental registration under very limited circumstances: all personnel must be working in the same location, all protocols come up under the department, there is a department chair responsible who has the authority to exercise control and accountability to him/her, (s)he is willing to accept the responsibility for the Controlled Substance registration etc. There should be no loaning or swapping of Controlled Substances between researchers.

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Individual registration and licensing is required for use of Schedule I controlled substances without exception.

DHHS will only issue registrations to those that have an approved IACUC protocol- they don’t want copies of the protocol with the registration form but may want to see it for the inspection. They will reference it by number in their report. (If a PI has more than one protocol, all protocols may be covered under the same registration. List drugs in all the protocols on the registration form and have copies of all relevant protocols for the inspection.)

State license:
At this time, the NC-DHHS, Drug Control Unit does not have a Webpage or online information available. Contact the NC-DHHS, Drug Control Unit by phone at 919-733-1765 (Ms. Joi Baker) in order to begin the registration process and address questions about the application. The state requires that registrants fill out the DHHS 225 form (for researchers and analytical laboratories).

Complete North Carolina Department of Health and Human Services (DHHS) Form 225. Submit DHHS Form 225 to the address listed on the form. [http://research.unc.edu/ccm/groups/public/@research/@iacuc/documents/content/ccm3_031058.pdf](http://research.unc.edu/ccm/groups/public/@research/@iacuc/documents/content/ccm3_031058.pdf)

In order to properly complete this form, you must know which schedule(s) your controlled substance(s) are in, and whether they are narcotic or non-narcotic (required for Schedule II and III substances only). You can find this information in Appendix 9-A of the EHS Laboratory Safety Manual. [http://ehs.unc.edu/manuals/docs/lab_safety_manual.pdf](http://ehs.unc.edu/manuals/docs/lab_safety_manual.pdf)

The state licensing requires the registration fee at the time of submission. The state licensing fee may be paid from departmental funds, non-federal funds, or personal funds. You cannot use federal grant funds (e.g., NIH funds) to pay for the controlled substance registration (NIH Grants Policy prohibits the use of federal funds for the controlled substance registration).

The registration fee is currently $125 for researchers and $100 for analytical laboratories. Annual renewal: $125 (Due date for all annual renewals is October.)

An agent of the DHHS will contact the applicant and schedule an inspection of the proposed holding location. Inspections are generally an on-site physical inspection of your controlled substance box and log books prior to receiving your registration. Because the on-site inspection can take significant time to arrange, most state licenses take about 3 months to be completed.

For other questions concerning the state process, contact the DHHS at: Department of Health and Human Services 3008 Mail Service Center Raleigh, North Carolina 27699-3008 Telephone: (919) 733-1765

Federal license:
Once the state license has been issued by NC DHHS, the Federal license can be obtained. (The federal office will not process an application for federal registration until DHHS has issued

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a state controlled substance registration number.) Include the NC license number on the Federal form. Since NC has already inspected, the DEA agent will most likely accept that and it will only take about another 2 weeks for the federal license. (The possible exception is for Schedule I substances- federal agents generally require a physical inspection for all Schedule I substances.)

For Federal registration, researchers and analytical laboratory personnel must complete the DEA Form 225 for new applications, or the Form 225-A for renewal applications.

The DEA preferred option is to file on-line.

If you choose the hard copy option, mail paper copies to:
Drug Enforcement Administration
Registration Section/ODR
P.O. Box 2639
Springfield, VA 22152-2639

A copy of the DHHS registration must be available for review. A copy of the IACUC approved protocol which requires controlled substances must also be available for review. (If a PI has more than one protocol, all protocols may be covered under the same registration. List drugs in all the protocols on the registration form and have copies of all relevant protocols for review.)

Because UNC is a state institution, UNC personnel are exempt from the Federal registration fee.

Annual renewals are due on the anniversary of the initial approval. Procedures for applying for the annual renewal are the same as the original registration (a re-inspection of the holding location is not routinely performed).


Once registration at the State and Federal level is complete, and you have passed a background check and received your licenses for controlled substances, you can proceed to ordering. Note that the NC-DHHS, Drug Control Unit and the DEA can (and often do) send out inspectors to verify that adequate security is in place before they issue the licenses. For ordering Schedule I and II substances, you must use the Official Order Form – DEA 222. https://www.deadiversion.usdoj.gov/webforms/orderFormsRequest.jsp

You can obtain these forms free of charge from the DEA Greensboro Field Office: You can also contact the Field Registration Technician at the DEA Atlanta Regional Office at (1-888-219-8689) to obtain Official Order Form – DEA 222, or for any questions about registration.

Security
The registrant is responsible for managing the controlled substances in accordance with all regulatory requirements including security, inventory, and recordkeeping.

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(1) Facility Security
Regardless of schedule, all controlled substances must be kept under lock and key, in a substantially constructed cabinet or safe, and accessible only to authorized personnel. Controlled substances should be maintained behind a minimum of two locks (ex. a locked container inside a locked cabinet or a locked cabinet in a locked room. NOTE: The 'locked room' must always be locked when it is not occupied by either the registrant or an authorized user.)

In select circumstances, a securely affixed single locked device may be approved by the DHHS inspector. Storage cabinets must be heavy enough to be essentially immovable, or built into the structure of the building. Doors must not be prone to forced opening by prying tools, or easily removable at the hinges. Wood or laminate casework is not likely to provide adequate security.

Locks may be combination locks or key locks (key locks are preferred). Combinations or keys must not be readily accessible to individuals not on the ‘Authorized Users’ List. If key locks are used, then the two locks must be keyed differently, the two keys must not be stored together (not on the same ring) and both keys must be safeguarded and not accessible to unauthorized users.

Keep the controlled substances locked in their storage locations except for the time required for authorized staff to remove, work with, and replace them.

Schedule I and II substances have the highest security requirements, and must be stored in an approved safe, steel cabinet, or vault. There are specific facility security requirements for researchers and analytical laboratory personnel who are not practitioners versus practitioner requirements.

Please contact EHS if you have questions about whether your facility security is adequate.

(2) Personnel Security
For substances in Schedules II-V, the registrant may authorize additional personnel to use the substances for approved activities. The registrant is required to screen these employees prior to authorization, using the following questions for non-practitioners who seek access to DEA controlled substances (ref. 21 CFR 1301.90):
--Within the past five years, have you been convicted of a felony, or, within the past two years, any misdemeanor, or, are you presently charged with committing a criminal offense?
--In the past three years, have you knowingly used narcotics, amphetamines, or barbiturates other than those prescribed to you by a physician?
--Have you had an application for registration with the DEA denied, revoked, or surrendered for cause?

Registrants must maintain the answers to these screening questions for authorized personnel in a secure place, away from the purview of unauthorized personnel. Schedule I substances may not be issued to anyone other than the registrant, or used by anyone other than the registrant. If additional personnel need to use Schedule I substances, they must individually register with NC-DHHS, Drug Control Unit and DEA.

Inventory and Recordkeeping
Registrants must maintain complete and accurate inventory records for all controlled substances. These records must be in or near the primary work area, separate from all other records and documents, and available for inspection during regular work hours. (Maintain all of the below-referenced records for a period of at least three years from the date of the last entry. In the event of an audit by DEA or NC-DHHS, Drug Control Unit, you will need to produce these records.)

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Records must include records of receipt, use, and inventory.

Receipt of Controlled Substance: A separate and current record indicating the date received, name and address of supplier, the type, strength, and concentration of substance, and the amount received. The person receiving the substance must sign each record. Document and rectify discrepancies prior to using the substances; report discrepancies to the seller immediately. A copy of the DEA Form 222 MUST be used to document initial quantities (or quantities added to the cabinet); maintain forms and reports in a log book.

Sign, date, and maintain the original documents (e.g., packing slips, receipts) for three years. All receipt, discrepancies, or other documents must be maintained in a log book.

For Schedule I controlled substances, the Registrant must receive the controlled substance. Authorized Users may not receive Schedule I agents.

For Schedule II-V controlled substances, the Registrant or Authorized User (if approved by a Power of Attorney) may receive controlled substances.

When receiving Schedule II substances, sign the Form 222 and keep the “blue” page for your controlled substance records. The remainder of the form 22 is remitted to the vendor for their records. This form must be maintained in the registrant's Controlled Substance files to serve as the source document for receipt of the controlled substances. Note that blank 222 forms should be securely locked where they may not be obtained. These are controlled documents. Form 222 are sequentially numbered, assigned to a specific registrant, and must be ordered from the DEA on-line.

Use of Controlled Substance: A separate and current record for the storage and use of each controlled substance, indicating 1) the name of the substance, 2) source of the substance, 3) date of expiration of the substance, 4) date of receipt, 5) unique identification number for the bottle, 6) starting quantity, 7) use date, 8) building and room, 9) specific research experiment or analysis (protocol), 10) animal (or group of animals) it is used on, 11) person dispensing the medication from storage, 12) person administering the medication to the animal(s), 13) type and strength used, and 14) the quantity used. Each use is a subtraction from the starting quantity, and the running amount must equal the total amount remaining. The person working with the substance must sign each record of use. Because these records require subtracting balances as the substances are used, they are often called “substance balance log sheets”. See Appendix 9-C in the EHS Lab Safety Manual for an example of a substance balance log sheet. http://ehs.unc.edu/manuals/docs/lab_safety_manual.pdf

Certain controlled substances (e.g., diazepam [valium] and similar agents) should not be stored in a plastic container such as a syringe, as plastic degrades the agent and will render it ineffective. Always confirm the appropriate storage container prior to use.

Schedule I substances require a bound book rather than a loose leaf or 3-ring binder. A 3-ring binder is recommended for maintaining all records for Schedules II-V controlled substances.

Labeling: Each bottle (or box) of controlled substances must be individually identified by a unique number. Original packaging showing the product information should be used when possible. Controlled substances containers (vials, ampoules, or boxes) may be removed from the original packaging if the interior container has been labeled to include the name of the controlled substances, the lot number (or unique identifier), the final concentration, the amount per container, and the expiration date (either as per the manufacturers recommendations or the most recent expiration date of the combined substances, if mixed).

If syringes are filled and stored in the controlled substance cabinet; or if controlled substances are compounded, diluted or combined, each container must be labeled and tracked. The label must include 1) the name of the controlled substances, 2) the lot number (or tracking number) of
the product, 3) the date reconstituted (powders) or combined/mixed (see below), 4) the final concentration, 5) the amount per container, and 6) the expiration date (either as per the manufacturer’s recommendations or the most recent expiration date of the combined substances).

Mixtures: When mixing substances (e.g. ketamine & xylazine), you can 1) completely use the mixture during that day with no 'left-overs, 2) almost completely used during that day and the remaining quantity disposed of as waste, 3) maintain the mixture for subsequent use. In the latter case, the mixture must be tracked using the Record of Controlled Substance Administration/Dispensed – Combination Drug. Expirations of mixture should be recorded either as per the manufacturers recommendations or the most recent expiration date of the combined substances.

Inventory of Controlled Substance: In addition to the balance log records, initial and biennial inventory records are required for Schedule I and II substances. The registrant (or their designee) must audit the controlled substance cabinet and the records of dispensing at least once every two years. These shall include the name of each substance, each finished form of the substance (solid, tincture, inhalant, etc.), the number of units or volume of each finished form, and the number of containers of each finished form. After auditing, the auditor will record whether the inventory was accurate (record name of auditor and date of audit) or, if there were discrepancies, define them. The auditor must then include their signature. Damaged, defective, expired, or impure substances awaiting disposal must be included in the inventory until they are disposed. See Appendix 9-D in the EHS Lab Safety Manual for an example biennial inventory sheet for Schedule I and II substances.


Federal and state audits may occur at random intervals determined by the state or federal agency. Annual audits should be expected by the registrant. Effective management of controlled substances by controlling access, recording use, documenting disposal, and auditing the process, decreases the likelihood of problems being found during a state or federal audit.

Loss, Theft, or Misuse
In the event that controlled substances are lost, stolen, or used in an unauthorized manner, the registrant must immediately contact the UNC Police at 962-8100 (or 911), and the DEA Office of Diversion Control in Greensboro, phone number 336-547-4219. The DEA staff will let you know whether you need to fill out a copy of DEA Form 106: Report of Theft or Loss of Controlled Substances. Complete Form 106 online and submit electronically via the internet to DEA Headquarters. Instructions for completing the form are online. Print a copy of the completed form to keep with your records. Also, DHHS requests you send a copy to them, though this is not a requirement. Diversions are likely to trigger audits. Please follow the facility and personnel security measures outlined above to reduce the chances of loss, theft, or misuse of controlled substances.

Revisions to Anesthetic/Analgesic Protocol
Once a registration has been approved, it can be revised to add individual controlled substances due to a modification of an anesthetic plan or euthanasia agent. The IACUC protocol(s) must also be amended to include the additional anesthetic plan or euthanasia agent as well. Both the NC state DHHS and federal DEA registrations must be modified:

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The NC state DHHS registration should be revised first. The request should be emailed to the DHHS (joi.baker@dhhs.nc.gov). Provide the following information: 1) Registrant name and contact information, 2) Registrant DHHS number, 3) Registrant DEA number, 4) name of drug to be added, 5) drug code and schedule of drug to be added, 6) Reason for addition of the new controlled substance(s).


If the registrant is already approved for the same schedule drug as being requested, they will receive a confirmation email from DHHS noting approval of the additional controlled substance(s). If the registrant is not already approved for the schedule of drug being added, they will receive a confirmation email from DHHS noting approval of the additional substance(s) as well as a modified registration form with the updated schedule for retention by the registrant.

If a registrant is approved for schedule II-V controlled substances and wishes to add a schedule I agent, a separate registration is required for the schedule I agent.

The federal DEA registration should be revised once approval for the additional controlled substances has been approved by the DHHS. The registrant should contact the DEA office directly at 336-547-4219 and ask to be directed to a DEA agent regarding the addition of controlled substances to an existing research registration. The DEA agent will provide specific details regarding submission of the necessary documentation for the request. The registrant should be ready to provide the document submitted to the DHHS (above), the DHHS email reply approving the addition of the controlled substance(s) to the state registration, and the revised state registration form if applicable.

If registrant is not already approved for the schedule drug requested, then once approved a revised copy of both DHHS and Federal registration should be sent to vendors prior to ordering of the controlled substance/drug.

Disposal
You must account for all controlled substances upon their disposal. Substances must be stored under lock and key until ready for disposal.
For unused, leftover substances (considered contaminated after removal from bottle/container) the registrant may dispose of the substances by injecting the substances onto absorbent material (ex. soda-sorb, cat litter) and discard via trash. (For substances that do not pose an ecological hazard -e.g. pure substances not commingled with other waste types-, the registrant can dispose the substances down the sanitary sewer with a witness present.) Note that only the registrant or his/her authorized agent can do this. Every disposal must be witnessed. Destructions must be documented on the DHHS form.

For expired or unused bottles of substances, registrants may use the Reverse Distributor System. While there is no specific definition for what must be disposed via the Reverse Distributor process, generally this applies to multiple bottles of controlled substances which may be excess or expired. Registrants must contact a DEA certified reverse distributor for disposal.
In North Carolina, the approved reverse distributors are:
ALMAC Clinical Services Inc – (919) 479-8853
DCM Ventures, Ltd. dba RXNET Services – (336) 273-5112
Healthcare Waste Solutions dba BMWNC – (704) 821-4766
Medcycle – (336) 510-4970
Pharmaceutical Dimensions – (336) 664-5287

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Every disposal must be witnessed. The registrant and witness must sign DEA Form 41 stating the date of disposal, the type/quantity of substances disposed, and the method of disposal. Fax a copy to the DEA Office of Diversion Control in Greensboro (fax 336-547-4209). As with other records, keep a copy for at least three years. The registrant or his/her authorized agent must perform the disposal. If the registrant is not available to perform the disposal (for example, the registrant has left the institution, or is deceased), contact the NCDHHS, Drug Control Unit at 919-733-1765 or DEA Diversion Control at 336-547-4219 for guidance. For controlled substances that are converted into a non-recoverable hazardous waste mixture, contact the Hazardous Materials Manager at 962-5509 for advice on disposal.

Transfers
License holders who wish to transfer these substances to a designated authorized user can do so, but the license holder retains all liabilities for loss, theft, or misuse of the substance. DEA Form 222 is required for any transfer of Schedule II substances between researchers. Requisition forms are used for transfer of Schedule III – V substances (provides documentation of legal transfer). (Registration is not transferrable. Do not attempt to transfer or re-assign the registrant role.)

Cancelling a registration
If a registrant no longer requires the controlled substance or is no longer a UNC employee, the registrant must dispose of controlled substances (as outlined above) or transfer controlled substances, to another approved registration. Should the PI be relocating to continue their research at another location or institution, they can transfer their drugs from their UNC registration to their new registration at the other location once approved. A separate new registration is required for a change in location, even when the registrant will be the same and use the same drugs for the same purpose. The registrant should notify the DHHS to terminate their registration and also notify the DEA to terminate their registration.