Mass General Brigham
Mass Eye and Ear

# Use of Controlled Substances in Non-Human Research: Standard Operating Procedures

## Overview

At Mass Eye and Ear (MEE), investigators often use controlled substances when carrying out their non-human research protocols. Due to their potential for abuse, each investigator is responsible for procuring, securing, monitoring and disposing of controlled substances in accordance with federal and state laws and hospital policy. The purpose of this Standard Operating Procedure is to provide guidance for implementing the Mass General Brigham Use of Controlled Substances in Non-Human Research Policy.

## Controlled Substance Determinations

To determine if the substances you are using in non-human research are covered by the federal and/or state regulations, consult the list of controlled substances covered by the federal regulations and the Drug Enforcement Administration (DEA) schedules found at: Controlled Substances Schedules

If the substance is not included in the DEA list, then it is not controlled by federal regulations and a DEA registration is not needed. However, Massachusetts Department of Public Health (DPH) considers all prescription drugs which are not included in DEA Schedules I –V as Schedule VI drugs and use of these requires a Massachusetts Controlled Substance Registration (MCSR).

## Registration

It is the Principal Investigator's responsibility to obtain appropriate licenses and registrations. Research-specific licensure is required and is separate from your practitioner licensures. All research investigators using Schedule I-V Controlled Substances for their non-human research must obtain a research-specific Massachusetts Controlled Substance Certificate (MSCR) and a Drug Enforcement Agency (DEA) Registration. For Schedule I Controlled Substances, you are required to have a separate registration from the Schedule II-V Controlled Substances for both DPH and DEA. If your research requires the use of substances solely included in Massachusetts Schedule VI, then you will only need to obtain a MCSR. This includes drugs ordered through chemical companies without prescription.

Licenses/registrations are issued to an individual who may authorize other individuals to operate under the license; are limited to specific drugs and drug schedules identified on the license; and are issued for a specific location where the controlled substances are to be delivered and stored. Any changes to the location must be amended through a submitted update. Registrations must be renewed each year.

To register, researchers must complete and submit the following **in the order listed**:

1. Massachusetts Controlled Substances Registration (MCSR) (State)
2. DEA Form 225 (Federal)

Once the application is received by the DEA, they will send you a "Researcher Survey" that must be completed and returned. For new applications, the DEA will conduct an interview and site inspection. Research Compliance must be present for this meeting.

### Authorized Users

The Registrant has ultimate responsibility for ensuring proper acquisition, use, storage, and accountability of Controlled Substances; however, the Registrant may authorize members of his or her laboratory to work with Controlled Substances by including those individuals on their DPH registration application. An Authorized User must have a reporting relationship, funding relationship, or have a protocol in common with the Registrant. For purposes of DEA Compliance, Authorized Users must be documented on the Authorized Users Log in the Controlled Substances Accountability Logbook. All Authorized Users must be a current MEE employee with a valid MEE badge.

If an individual needs to be removed or added as an Authorized User after the time of initial application, the Registrant must update the Authorized User Log in ythe MGB Controlled Substances Accountability Logbook. Registrants are required to keep and maintain an updated Authorized User Log as part of the controlled substance documentation in a 3-ring binder.

## MGB iLog Controlled Substance Registration

Upon approval by the DPH and DEA, Registrants must create and maintain a registration in the MGB Controlled Substances database iLog. The Registrant must originally create the account as it is tied to their MGB credentials. Once the account has been created, the Registrant can grant access to Authorized Users to make updates or add information to iLog.

The Registrant must enter the registration numbers for their MCSR and DEA registrations, including their expiration dates. Additional information that is required includes inventory date, approved schedules, controlled substances used, location, authorized usernames, and lab contact (not required). A lab contact is an individual that will receive reminder notices but will not have authority to make changes. In order to save the record, copies of the registrations must be uploaded, and the date of the last inventory must be entered.

iLog is designed to send reminders for registration expiration and inventory due dates. Other functions in iLog include being able to request disposal, notify Research Compliance of a DEA visit, submit a notification of loss or stolen substances, and contact Research Compliance.

## Ordering

Once registrations have been granted from the state and federal agencies, Registered Investigators who wish to purchase Schedule I-V substances may purchase their own supply of Controlled Substances via MGB Supply Chain. All orders for controlled substances must be placed by the Registrant or an Authorized User. Schedule I and Schedule II controlled substances must be ordered and received by the Registrant. Schedule III-V controlled substances can be ordered and received by the Registrant or an Authorized User.

Registered Investigators are required to establish accounts with the appropriate vendors of Controlled Substances. To create an account, Registered Investigators should send the following documents to Paul Donahue in Materials Management (pwdonahue@mgb.org):

- Completed New Account Setup form
- Copies of their DEA and MCSR registrations

Once an account has been set up, Registered Investigators must complete their Purchase Requisition through MGB e-Buy. Information on completing requisitions is located on the MGB web site: http://supplychain.partners.org/. **Please remember**, the shipping address **must be** the same as the address on your DEA Registration

- DEA Controlled Substances must be ordered as a Special Request and **not** through the PHS eBuy search catalog
    - Controlled Substances should be ordered separately from other items (e.g. supplies)
    - In the description line, the brand and the name of the drug along with the concentration should be recorded (e.g. Ketaved, Ketamine, 100ml/mg).
    - The comments section of the eBuy order should include:
        - Name of DEA license holder
        - DEA registration number
        - Name and telephone number of an Authorized Designee authorized to pick up the order (if applicable)
- Send the completed eBuy requisition, along with copies of your DEA and MSCR registrations, to MGB Supply Chain (Fax: 617-623-5471)
- Purchasing will convert the eBuy requisition to a Purchase Order

- For CIII-CV Controlled Substances:
  - Supply Chain will generate a PO number and place the order
  - Drugs will be shipped directly to the address listed on the USDEA registration
- For CI and CII Controlled Substances:
  - Supply Chain will send the PO back to your lab
  - You must mail a hard copy of the PO directly to the company, along with the completed DEA 222 form. You must keep the Purchaser's (blue) copy of the 222 where it can be easily retrieved as needed during inspections.

### Completing the Official DEA 222 Forms

- When ordering Schedule I & II Controlled Substances, you are responsible for filling in the number of packages, the size of the package, and the name of the item.
- Each Official Order Form must be signed and dated by the person authorized to sign a registration application.
- When the items are received, the receipt must be documented on the purchaser's copy (copy 3) with the actual number of packages received and the date received.
- Proof of receipt must be kept with the purchaser's (blue) copy of Form 222 so it can be readily retrieved when requested.

### Ordering additional DEA 222 Forms

- DEA Controlled Substance Official Order Forms (DEA 222) for Schedule 1 & 2 Controlled Substances can be ordered at: https://www.deadiversion.usdoj.gov/webforms/orderFormsRequest.jsp.
- The DEA 222 Order Forms may also be ordered by calling the DEA Headquarters Registration Unit toll free at 1-800-882-9539 or the nearest DEA Registration Field Office. The forms will be mailed within 3 working days.
- There is no charge for Official Order Forms

## Receiving

By law, controlled substances can only be shipped to the address listed on the DEA registration. Orders are received from the vendor at the loading dock that corresponds to the shipping address, i.e. 243 Charles St or 20 Staniford St. Once the package is received, Receiving will contact the Registered Investigator and/or Authorized Designee. If the Registered Investigator/Authorized Designee is not available, the package will be secured in a locked cabinet in a locked office in the receiving area. The Registered Investigator or Designee will need to show their MEEI/SERI ID when picking up Controlled Substances and sign for the order.

Upon receipt of the controlled substance, the Registrant or designated Authorized User must immediately record the controlled substances into the Controlled Substance Accountability Logbook in the Controlled Substance Inventory Log, label the container with the unique identifier, and secure the controlled substance(s) in the controlled substance storage cabinet.

## Storage

All Schedule I-V Controlled Substances must be stored in a secure, permanently affixed, substantially constructed double-locked drug cabinet or safe. Schedule I & II substances can be stored in the same safe or locked cabinet as Schedule III-V substances as long as access to that cabinet is restricted to individuals who are authorized to access the highest Schedule of drug maintained.

- For example, if Schedule II drugs are stored in a safe with Schedule III drugs, only people who are authorized to access Schedule I drugs can have access to the safe

Schedule VI Controlled Substances must be stored in a limited access area out of the public eye, but not in the Controlled Substance cabinet.

Access to drug cabinets and safes must be restricted to only Registered Investigators and Authorized Users who are listed on the registration applications submitted to DPH and DEA. Authorized User logs should be reviewed and updated regularly.

All Schedule I-V Controlled Substances should be maintained in the locked storage location except for the actual time required for Authorized Users to remove, legitimately work with, and replace the Controlled Substances. No Controlled Substance should be left unattended at any time.

Inventory of Controlled Substances kept on site should be limited to the smallest quantity required to effectively conduct the indicated research. It is strongly recommended that any diluted substances or mixtures be prepared at the time of administration to the animal to ensure their effectiveness. All prepared dilutions and mixtures must be kept in the locked cabinet when not in use. Any prepared dilution or mixture not used on the same day must be listed separately on a Controlled Substance Disposition Log page in the MGH Controlled Substance Accountability Logbook.

Access to the drug cabinet must be limited to the Registered Investigators and Authorized Users. Keys and combinations to drug cabinets or safes should be secured in a locked cabinet or drawer in an office. Only the Registrant and Authorized Users should have access. Keys should never be left unattended in an unsecure location.

## RECORDKEEPING AND INVENTORYING

### RECORDKEEPING

To maintain compliance with State and DEA requirements, it is **required** to use the MGB Controlled Substance Accountability Logbook ('MGB Logbook') to document Controlled Substances. The MGB Logbook must be secured to limit access. Storage can be in the Controlled Substances locked cabinet or safe or locked in a nearby cabinet/drawer.

MGB Logbooks should be kept separately for Schedule I, Schedule II, and Schedule III-V Controlled Substances. All records relating to controlled substances must be kept and maintained by the Registered Investigator for at least two years. They must be readily retrievable and are subject to audit. The following requirements apply to the MGB Logbook:

- Only one container can be documented per Controlled Substance Disposition Log page
- Secondary containers (diluted substances or mixtures) must be logged and accounted for on a separate page from their original source container if the secondary drug is not completely used
- The last line of the log must always equate to the amount of Controlled Substance remaining in the Controlled Substance cabinet

Registered Investigators are required to maintain the following documentation:

- **MGB Logbook**
- **Controlled Substances Procurement Forms**: DEA Form 222 and any receipts, invoices, packing slips, PO.
- **Quarterly inspection records**
    - All Registered Investigators are required to conduct self-inspections on a quarterly basis to ensure that the Controlled Substance Disposition Logs match the physical inventory. Quarterly inspections should be documented using the Controlled Substances Inventory Log in the MGB Logbook. Inspection forms should be reviewed and approved (signed) by the Registered Investigator.
- **Biennial Inventory**: By law the Registered Investigator shall take a separate inventory of all controlled substances on hand biennially. Biennial inventory should be documented on the DEA Inventory Form in the MGB Logbook.
- **Report of Theft or Loss**: DEA Form-106
- **Any Drug Disposal Form**: DEA Form-41
- **DEA registration certificate**: DEA Form 223
- **State registration certificate**: MCSR

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## Primary and Secondary Containers

Primary containers must be logged in the Controlled Substances Disposition Log contained within the MGB Logbook. Only one container can be logged per page. The primary container must be labeled with a unique identifier that is recorded in the log and written on the bottle (e.g. Ketamine = K1 for the first bottle, K2 for the second bottle, etc.)

If a Controlled Substance is removed from the primary container and placed in a secondary container to be altered, and the altered substance is not completely used, it must have a unique identifier (e.g. Ketamine/Xyalzine = KX1 for the first container, KX2 for the second container, etc.) and must be tracked separately on a Controlled Substance Disposition Log page in the MGB Logbook. This secondary container must be stored in the Controlled Substance cabinet. The circumstances which would require that the Controlled Substance received from the manufacturer be altered in some way for the purposes of the research are:

- Reconstitution: When the Controlled Substance received in a powdered form and sterile saline is being added to return it to liquid form.
    - Example: Telazol is reconstituted with sterile saline.
- Mixture: When a Controlled Substance is mixed with another Controlled Substance or Schedule VI drug.
    - Example: Ketamine is mixed with xylazine.
- Dilution: When a Controlled Substance is too concentrated to dose due to the size of the animal so sterile saline is used to reduce the concentration.
    - Example: Buprenorphine is diluted with sterile saline.

Secondary containers used for altered Controlled Substances must be:

- Sterile
- Labeled with the following:
    - A unique identifier
    - Formulary of drugs in the container
    - Date the solution was prepared (substance altered)
    - Expiration date
    - Initials of individual that prepared solution

The formulation details of the altered controlled substance must be provided on the Controlled Substances Disposition Log for the secondary container.

The expiration dates will change when the controlled substances are altered. Use packaging instructions to determine the expiration dates when possible, including storage requirements. Secondary containers must be sterile to consider storing for later use. The following is guidance if there are no packaging instructions:

- Reconstituted solutions must be discarded per packaging instructions. Be sure to review the storage requirements.

  *For example: TELAZOL should be stored at controlled room temperature 20° to 25°C (68° to 77°F) prior to use. After initial use, discard unused solution after 7 days when stored at room temperature or after 56 days when kept refrigerated.*

- Mixtures must be discarded 30 days after initial preparation, or sooner if the mixture becomes clouded or contaminated.

- Dilutions must be discarded 30 days after the initial mixing date.

An example for labelling secondary containers follows:

Ketamine/xylazine mixture:

KX1
1ml = Ketamine @ # mg/kg and xylazine @ # mg/kg
Prep: 9/1/15 Exp: 10/1/15 Initials: AB

### Inventory

Per DEA regulations, an initial inventory must be performed for all new registrations upon registration approval. Initial inventory should be documented on the DEA Inventory Form in the MGB Logbook. Two signatures are required on each completed DEA Inventory Form: the person who completed the inventory and a witness to the process.

- Initial inventory **should be zero**, as there should be no Controlled Substances on hand.

Upon receipt of the first order, a second DEA Inventory Form should be completed with the new Controlled Substances that were received.

Two years from the date of the receipt of the first order, a biennial audit should be conducted and repeated every two years afterward. The inventory should only include Controlled Substances that are currently in the Controlled Substances cabinet at the time that the inventory is performed. This includes any expired Controlled Substances that are waiting to be destroyed.

To complete the form:

- For Schedule I and II Controlled Substances, identify each unit individually and notate *the exact amount* contained in each container
- For Schedule III-V Controlled Substances, identify and notate the total quantity of all units to the nearest unit (weight or volume)
- **Do not** include DPH Schedule VI drugs. Schedule VI drugs **should not** be stored in your Controlled Substance cabinet.

### Massachusetts Schedule VI

Schedule VI drugs consist of all prescription drugs, which are not included in DEA Schedules I -V. When ordering through an approved vendor, this is indicated as “Rx only.” If ordering through a chemical company a prescription may not be required but the order will still require a Schedule VI MCSR.

Schedule VI drugs are not required to be stored in the same way as DEA Schedules I-V. An example would be to store the prescription drugs in a locked cabinet or drawer in your locked laboratory. Schedule VI drugs cannot be stored in your controlled substances storage cabinet.

It is also not necessary to document the use of Schedule VI as you would DEA Schedule I-V. Do not use the MGB Logbook to document DPH Schedule VI drugs. However, you should still have a system that allows you to “deter and detect diversion.” An example would be keeping a log to document order, receipt, and usage.

## Theft, loss, or unauthorized use

Any loss of a Controlled Substance, including theft, suspected theft, unauthorized use, or other loss must be reported immediately in iLog or directly to Research Compliance.

If you are unsure as to whether a loss has occurred, contact Research Compliance for consultation. Research Compliance will collaborate with others as needed to determine if the concern is a reportable event and ensure external reporting requirements are met.

- USDEA requires reporting within (1) business day of discovery by completing the DEA Form 106
- We must immediately report the incident by telephone to the MA Drug Control Program (DCP) at (617) 973-0800 and then must follow up with a written report within 7 days of discovery.

In addition, any unauthorized persons who gain access to Controlled Substances for the purpose of diversion or theft may be reported to MEEI Security and the local Police Department and may be subject to disciplinary action.

## Disposal

Should a researcher be in possession of expired or expiring drug products, the Registered Investigator or

Authorized User must mark the containers clearly as "NOT FOR USE". Any drugs marked "NOT FOR USE" must be stored separately from non-expired drugs but still in the locked drug cabinet or safe. A different shelf in the drug cabinet or shelf or a bin or container placed in the drug cabinet or safe can be used for storage as long as they are clearly marked "NOT FOR USE- EXPIRED DRUGS".

All expired drugs should be disposed of as soon as possible. Controlled Substances disposals are scheduled quarterly by MEE Materials Management who will communicate the disposal dates to the research community. You must complete the required DEA 41 Form prior to the scheduled disposal. In addition to the DEA 41 form, you must document the disposal in your MGH Controlled Substance Accountability Logbook on the Disposition Log. Disposal process requires supervision from two MEE representatives as witnesses (the Registrant/Authorized User and another representative) in collaboration with the third-party waste contractor (e.g. Triumvirate Environmental Inc.). If you need to dispose of any controlled substances outside of the scheduled times, please contact MEE Materials Management and Research Compliance to coordinate.

**Controlled Substances can NOT be abandoned or discarded through the regular trash, biohazard bins, or down a sink, floor drain, toilet, or any other plumbing fixture.**

The registrant must account for the disposal on the Controlled Substances Disposition Log, including the disposal of residual amounts. All records concerning the disposal of Controlled Substances, including DEA form(s) 222, if applicable, and/or DEA Form 41, must be maintained by the registrant in a secure location (with the logbook is recommended) for two years after the end date of the logbook.

## Abandoned Drugs

Any Controlled Substances for disposal that cannot be linked back to an active DEA registration shall be considered "abandoned" or "orphaned" and shall be identified as such in notification to the DEA and any other associated documentation. Abandoned or orphaned drugs can arise after a lab clean-out, transfer, or closing when the DEA registrant did not dispose or transfer the Controlled Substance appropriately prior to departure. Reasonable efforts should be made by the department responsible for the lab, in collaboration with MM and Research Compliance, to determine who the substance(s) belongs to and if it can be traced to an active DEA registration. If the Controlled Substance(s) can be traced to an active registrant, then it is the responsibility of that registrant to dispose of the Controlled Substance(s) properly.

If the Controlled Substance is truly abandoned or orphaned (i.e. no connection can be made to a DEA registrant), then MM shall:

- Contact the third-party waste contractor for disposal
- Contact Research Compliance to witness the disposal

## Record Retention

All documentation related to Controlled Substances must be maintained for two years after the end date of the Logbook.

## Lab Closures and Moves

### Registration

A registrant moving to a new physical location, within MEE, must request a modification of registration with DPH and DEA. The request and approval must be obtained from the state prior to making the modification with the DEA. Both approvals must be obtained before the controlled substances are moved to their new location. You must contact Research Compliance for assistance with relocating the Controlled Substances.

If you are moving to another location outside of MEE, you must apply for a new registration with DPH and submit a request for modification with the DEA to change the address. If you are moving to another location out-of-state, the new state must provide registration approval prior to submission to the DEA. The registrant should maintain

the new certificate with the old certificate until expiration.

If you are closing your lab and not transferring your registrations to another lab, you will need to notify DPH and DEA at least 30 days prior to closure.

- For DPH, you must notify them in writing and include the following in the notification:
  - Intended lab closure date
  - Description of controlled substances
  - Plan to destroy controlled substances
  - If you do not hear back from the DPH by the lab closure date, proceed as you described in your DPH notification request.
- For the DEA, contact the local DEA office to complete the DEA 104 Form for Voluntary Surrender of Certificate of Registration. The DEA will schedule a time to come on site to complete this form.

### Lockbox/Safe

If you are leaving the institution, all keys should be either given to the department chair or taped to the bottom of the cabinet only after all Controlled Substances have been disposed as described in the Disposal section of this document.

### Controlled Substances

If you are leaving MEE, DO NOT transport your Controlled Substances to your new location. All Controlled Substances must be disposed of as described in the Disposal section of this document. If transferring to a new location within MEE, Controlled Substances should only be removed from the cabinet during the process of the uninstalling/installing of the cabinet. During the time the Controlled Substances are out of the cabinet, the registrant or authorized user should maintain custody of the Controlled Substances. You must contact Research Compliance for relocation of the Controlled Substances.

### Logbook

If you are leaving the institution, contact Research Compliance at least two weeks prior to your departure to have your records reviewed. You are responsible for your Logbook and will take it with you.

## Forms

Massachusetts Controlled Substance Registration Form
https://www.mass.gov/how-to/apply-for-or-renew-a-podiatrist-optometrist-researcher-or-veterinarian-mcsr

DEA Form 225 (Research Registration)
https://www.deadiversion.usdoj.gov/drugreg/index.html

DEA Forms (222 - Order Forms; 41 – drug disposal/destruction)
https://www.deadiversion.usdoj.gov/online_forms_apps.html

DEA Registration Support -Toll Free Number: 1-800-882-9539