Introduction, Background & Terms

● Using Controlled Substances for Research

University of Minnesota research projects take many forms and focus on a variety of topics. Some research projects involve the use of controlled substances. When controlled substances are used for research, each individual who works on the project must be aware of and adhere to the Federal and State regulations and University policies that govern their use. This workshop will present an introduction to these regulations and policies, and an overview of the paperwork and record-keeping required for the use of controlled substances for research.

The **objectives** of this tutorial are to provide:

- An understanding of the Federal and State regulations for using controlled substances for research
- An understanding of the University of Minnesota policy for using controlled substances for research
- A detailed description of record-keeping requirements for using controlled substances for research
- A resource for researchers about the forms, instruction documents and other information available to help simplify compliance with the regulations and the University policy

● Background

A **controlled substance** is a drug or chemical whose manufacture, possession and use are regulated by the Federal and State government. This may include illegal drugs and prescription medications.
Controlled drugs are rated in the order of their abuse risk and placed in **schedules** by the Federal Drug Enforcement Administration (DEA)
The drugs with the highest abuse potential are placed in Schedule I, and those with the lowest abuse potential are in Schedule V. These schedules are commonly designated as C-I, C-II, C-III, C-IV, and C-V.
The mission of the **Drug Enforcement Administration (DEA)** is to enforce the controlled substances laws and regulations of the United States. The DEA is responsible for suppressing illegal drug use and distribution by enforcing the Controlled Substances Act. The DEA requires a registration for the possession and use of controlled substances.

● Terms Used in the University Policy

The University of Minnesota Administrative policy, *Using Controlled Substances for Research* contains several unique terms that form the structure of the policy. For each

of these terms, think about how it applies in your laboratory.

Authorized Users: Personnel who properly use controlled substances and maintain disposition records, and are allowed to perform activities with controlled substances as directed by the DEA Registrant. Must sign the Authorized Users Signature Log

Download Authorized Users Signature Log and complete the DEA-based questionnaire

for employee screening procedures as described in 21 CFR 1301.90

DEA Registrant: A University employee delegated by his/her department head to hold DEA registration, and is responsible for ordering, storing, using and disposing of controlled substances in his/her Unit. Also referred to as Unit Registrant.

Location: A room or designated area where controlled substances are stored or used. A location is managed by a single University employee, has a single address and has a DEA Registrant with which it is associated.

Unit: Any organizational entity within the University that has budgetary authority. Includes, but is not limited to, colleges, departments, centers, institutes, etc.

- ## Standard Operating Procedure

Controlled substances must be properly handled at all stages of purchase, use, storage, transfer and disposal. The Standard Operating Procedure (SOP) serves as a laboratory reference, and defines the person who is responsible for each of the activities related to using controlled substances for research. You may wish to bookmark the SOP for future reference.

Registering, Purchasing, Receiving, Labeling, Storing & Securing

● Registering for Controlled Substances

The DEA requires a registration for different types of activities when using controlled substances (e.g., research, teaching, clinical practice and other activities). **According to DEA regulations, the same registration to use controlled substances as a practitioner cannot be used to purchase controlled substances for research.**

Registrants are appointed by the Department Head and their numbers are limited by the Drug Enforcement Administration (DEA) to no more than one registrant per Department/Building.

Drug Enforcement Administration (DEA) Registrants must:

- Complete the Controlled Substance online training module
- Maintain a current DEA registration whenever controlled substances are being used
- Require any person that handles controlled substances to complete a DEA-based questionnaire
- Keep a record of the questionnaire until that person no longer handles controlled substances
- Authorize the purchase, use, and disposal of controlled substances
- Maintain an accurate list of authorized users of controlled substances
- Supervise the use of controlled substances
- Conduct a physical inventory of controlled substances at least every two years
- Maintain all records for at least three years

● Purchasing for Controlled Substances

The DEA and the University policy have specific procedures to be followed when purchasing controlled substances:

- The Registrant must be aware of all purchases of controlled substances. Provide an initial and dated copy of the purchase receipt to the Registrant.
- File the original purchase receipt with the location controlled substances records.
- Purchasing controlled substances from centralized sources is highly recommended for those on the Twin Cities campus.
- To pick up controlled substances, both campus pharmacies require a copy of the DEA registration, the Authorized Users Signature Log and photo identification.
- The purchase of C-I and C-II substances requires completion of a DEA Form 222. After the DEA has approved the use of C-I or C-II controlled

substances, they will send the Registrant the DEA Forms 222. After initial approval, additional Forms 222 may be requested from the DEA website.

● Receiving Controlled Substances

When picking up controlled substances from the pharmacy, or if controlled substances are shipped to the lab, ensure they are processed as soon as possible, by:

- Recording receipt of substances in the disposition record
- Locking controlled substances in the safe immediately

In addition, ensure that the purchase records:

- Initialing and dating purchase receipt
- Providing a copy for Registrant's records
- Filing the purchase records with laboratory controlled substances records
- If Schedule I or II provide copy of Form 222 to the Registrant. Keep the original with the controlled substances in the lab.

● Tracking of Controlled Substances

The Authorized User Signature Log, like all controlled substance records, must be kept for a minimum of three years. When someone leaves the laboratory, note the date the person departed on the log. If there is high turnover in the lab, a new log may need to be started. Originals of all Authorized User Signature Logs must be kept with the controlled substance records.

● Labeling Controlled Substances

All containers of controlled substances must be properly labeled. If the laboratory re-packages, compounds or dilutes controlled substances, appropriately label the re-packaged, compounded or diluted substance and ***store it in the safe***.

The label on diluted or combined controlled substances that will be stored at least overnight in the safe must include the following information:

- Name of controlled substance
- Schedule of drug
- Lot number
- Final strength or concentration of controlled substance
- Volume or amount of substance per container
- Date of dilution and initials/expiration date no more than 30 days after dilution

● Storing and Securing Controlled Substances

- Store controlled substances in a locked safe bolted to an immovable object.
- Store controlled substances ***separately*** from other drugs and materials.

- Limit access to the safe.
- For expired drugs, mark the container "Expired" and segregate in the safe.
- Complete a controlled substances disposal form and send an email to DEHS. Disposal procedures will be covered later.
- Store the slurry bottle with contaminated waste controlled substances in the safe.
- Store controlled substances requiring cold storage in a refrigerator or freezer with a locked door.
- Change the code whenever an authorized user leaves the lab

A safe with a digital electronic lock whose code can be re-set as laboratory staff changes is recommended. This also avoids the issue of key control. It is also necessary to have a separate safe for each Authorized User Lab.

Most electronic safes have an override key which should only be used in case of emergency if the battery runs down. Replace the battery immediately and secure the override key where only one or two Authorized Users have access to it.

Before purchasing a safe be sure that you pay attention to the safe dimensions as it relates to the amount of controlled substances you will store and the amount of space you have for installation. Be aware of how the door opens in relation to the installation site.
Many of the safes purchased to store controlled substances are small hand gun safes

Record-Keeping for Use of Controlled Substances

The University policy mandates the following about the use and record-keeping of controlled substances for research:

- Only Unit Registrants and Authorized Users may use controlled substances in the lab.
- The person using the controlled substances must be the one to initial and date the disposition record for the particular action performed. Every activity with controlled substances must be recorded on the disposition record, which is the primary record of all activities with controlled substances used for research. The recording requirements vary by the type of drug being used:
    - For C-III, C-IV and C-V drugs, the total volume used on a daily basis may be recorded on the disposition record. For instance, if 10 animals were given 0.3 ml of a substance on a specific day, the total in the disposition record could read 3.0 ml. However, the individual use must be recorded in a surgical, anesthetic or other research record that is accessible.
    - The regulations for use of C-II controlled substances (e.g. pentobarbital) are more stringent. Each individual dose must be recorded in the disposition record. In the instance of an animal surgery, the individual

recorded dose can be the total per animal per anesthetic episode. If an animal was given 1.0 ml of a substance and boosted with 0.5 ml three times during the surgery, the total individual dose would be recorded as 2.5 ml.

- The Controlled Substances Disposition Record form contains all the required elements from the DEA regulations, which are included at the top and bottom of the form:
    - Name of controlled substance
    - Concentration or strength
    - Form or type
    - Amount per container
    - Unit (DEA) Registrant's name
    - Lab location
    - Sequential page numbers
- If the recommended form is not used, all above required elements must be included in a modified form.

Using the Disposition Record for C-II Controlled Substances

A C-II controlled substance, the more stringent record-keeping requirements. For a C-II controlled substance, remember that the total use for each animal must be recorded individually. *For C-II drugs, do not combine the total use per day in multiple animals, as you can for C-III through C-V drugs.*

The disposition record is used to track all activities:

- Receiving
- Using
- Diluting or combining
- Disposing
- Transferring

Single Drug Disposition Record

Using the Single Drug Disposition Record is convenient when multiple animals are used and/or when other experimental information, e.g., animal weight, is needed. It is important to remember that with a C-II controlled substance like sodium pentobarbital you are required to record the drug use for each animal separately.

The following example demonstrates how to complete the Single Drug Disposition Record.

Controlled Substances Single Drug Disposition Record

Date: 3/12/09

Unit Registrant Name: Debbie Doe

Building and Room Location: 123 Mayo

Location of safe: 123 Mayo

Drug Name: Nembutal Schedule: II (I-V)

Lab reference number of original container(s) N/A

Form (liquid, tablets, patch, etc.): liquid

Concentration: 50 mg/ml

Expiration date: 4/6/09

Dilution or combination (mg/ml): 10 mg/ml <5x dilution with saline>

Total initial volume after dilution or combination: 2.5 ml

Date	Quantity used	Balance remaining	Use Information	Initials	Research information, e.g., animal wt
3/12/09	0.2 ml	2.3 ml	PAF study	JS	20 g
3/12/09	0.2 ml	2.1 ml	PAF study	JS	19 g
3/12/09	0.2 ml	1.9 ml	PAF study	JS	20 g
3/12/09	0.2 ml	1.7 ml	PAF study	JS	18 g
3/12/09	0.2 ml	1.5 ml	PAF study	JS	20g
3/12/09	0.2 ml	1.3 ml	PAF study	JS	21 g
3/12/09	0.2 ml	1.1 ml	PAF study	JS	20 g
3/12/09	0.2 ml	0.9 ml	PAF study	JS	19 g
3/12/09	0.2 ml	0.7 ml	PAF study	JS	20 g
3/12/09	0.2 ml	0.5 ml= to slurry bottle	PAF study	JS	20 g

Complete the required information at the top of the Controlled Substances Single Drug

Disposition Record.

In this example with diluted sodium pentobarbital, each of 10 mice received 0.2 ml, which leaves 0.5 ml diluted sodium pentobarbital remaining.

As noted on the disposition form, the 0.5 ml was put in the slurry bottle for disposal. The volume placed in the slurry bottle must also be recorded on the disposal form. (More information on the use of the disposal form and slurry bottle follows below.)

When large numbers of animals are used and the information is the same (e.g., euthanizing a large number of animals with the same dosage of drug), this record could be prefilled on the Single Drug Disposition Record. If this is done, the record must be printed and signed or initialed by the person performing the activity.

In addition, to save time or minimize duplication of recording, researchers may choose to use the Controlled Substances Single Drug Disposition Record as a surgical or procedure record by adding other research elements to the record. If this is done, file the original record with your research records and a copy in your controlled substances records.

Disposing of Controlled Substances

Substances to be disposed of must be kept in the safe until picked up by DEHS.

Dispose of expired and excess controlled substances in the original bottle. Mark the container “Expired” and segregate, if possible, from other controlled substances in your safe.

Small amounts of contaminated or waste controlled substances (i.e. in a syringe) can be collected and disposed of in a slurry bottle. A slurry bottle is a bottle that contains a contaminant.

Multiple types of waste controlled substances can be put in the slurry bottle. Schedule I and Schedule II waste should be kept in a different slurry bottle from Schedule III through V. The slurry bottle must be kept in the safe.

Record-Keeping for Controlled Substances Disposal

Each disposal into the slurry bottle must be recorded on the Controlled Substance Disposal Form which is used to record amounts of expired or waste controlled substances for disposal. It is also recommended that the amount placed in the slurry bottle is recorded on the disposition record. Completion of the disposal form is required by University policy.

To dispose of controlled substances using the Controlled Substances Disposal Form:

- Enter the DEA address as it appears on the DEA registration. The signature of the DEA registrant should be entered *at the time that DEHS disposal is requested.*
- All C-III through C-V controlled substances can be put in the same slurry bottle. DEHS is not registered to dispose of C-I controlled substances. An outside vendor must be used to dispose of C-I controlled substances. Contact DEHS for more information.
- The disposal form for the slurry bottle must have the total amount of each controlled substance contained in the slurry bottle until the research is completed. Keep adding to the slurry bottle until it is full. Remember to store the slurry bottle in the safe.
- More than one disposal form can be used for a slurry bottle as long as the pages are numbered in order.
- If you have expired drugs for disposal, use a separate disposal form and request that DEHS pick them up immediately.
- To request the disposal and pick up of controlled substances, email the disposal forms to DEHS and provide a contact name, phone number, and laboratory address. DEHS will arrange the pick-up.

Taking Inventory, Loss or Theft, Record Maintenance, Oversight

- ## Taking Inventory of Controlled Substances

  University policy requires that each Location using controlled substances for research must complete an inventory every two years. An inventory is the comparison of the quantity of controlled substances in the safe with the quantity written in the disposition records. These amounts should be the same.

  The Controlled Substances Inventory Record contains the required elements from the DEA regulations. The important requirements for taking an inventory are:

  - According to University policy, an inventory must be conducted at least once every two years.
  - The Unit Registrant files the original inventory with the Location records.

An inventory record for a laboratory with two of the most common controlled substances used for animal research at the University, sodium pentobarbital and ketamine.

The **Expected Amount** is found in your disposition record for each controlled substance.

The **Actual Inventory** is the amount counted in the safe. Be sure to use “mls” or “mg” for each entry. Unused lines are crossed out. Each entry is initialed and the inventory must be dated. If there is a discrepancy between the amount of controlled substances in the safe and the amount recorded, this discrepancy must be reported. Reporting requirements are covered below.

- ## Reporting Theft and Loss of Controlled Substances

  You will be asked to provide background information relating to this loss or theft incident, such as the date and place, the type (night break-in, armed robbery, etc.), and the estimated value of the controlled substances, etc.

- ## Procedures to follow concerning a loss of controlled substances:

  If there is an obvious or suspected break-in to your safe or other diversion of controlled substances, immediately contact the University Police

  If a discrepancy is identified during an inventory or other reconciliation:

  - The Unit Registrant must investigate the discrepancy.
  - The Unit Registrant must decide if it is necessary to use Form 106 to report the loss to the DEA.
  - If there is consistent loss of controlled substance that can be explained, write a memo to file with the controlled substance records that explains this consistent loss. An example would be loss in the hub of the needle that is consistent over a number of experiments.

- ## Maintaining and Retaining Records of Controlled Substances

  University policy have requirements for maintaining and retaining records about the use of controlled substances for research. These records include:

  - Authorized Users Signature Log
  - Copy of disposal records
  - Copy of purchase records: purchase receipts for all schedules for C-II
  - DEA registrations
  - Disposition records

Important points about **maintaining** records:

- The person performing the tasks (receiving, using, diluting, disposing) is responsible for documenting information on the disposition record.
- It is highly recommended that laboratory records be maintained in a three-ring binder so that nothing is lost or misplaced.

Important point about **retaining** records:

- Keep disposition records and other associated records at the Location for a minimum of three years according to the University controlled substances policy.
- NIH regulations or other sponsors may require a longer retention period.

● Oversight: Inspection and Compliance Reviews

Compliance reviews and inspections can happen at any time, and can be conducted by the DEA and University offices.

DEA Inspections can occur with or without notice. These inspections focus on storage, security and all controlled substances records.

Other University Inspections can be scheduled or unscheduled. These inspections will focus on security and all records of the Unit Registrants. Inspections may be conducted by the Institutional Animal Care and Use Committee (IACUC), the Office of Internal Audits, the Controlled Substances Manager, and others.