Overview of CSA Regulations for the Preclinical Research Environment

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CSA Regulations: Primary mandate is to prevent drug diversion

Some responsibilities rest with FDA (Controlled Substances Staff) and others with Department of Justice (DEA's Office of Diversion Control)

Legal "scheduling" of compounds is required by the CSA in a hierarchy for level of concern related to "abuse potential." FDA places compounds in one of the 5 Schedules based on an "8-Factor Analysis" mandated in the CSA.

1) Actual and potential for abuse, 2) Pharmacology, 3) Other current scientific knowledge, 4) History and current pattern of abuse, 5) Scope, duration, and significance of abuse, 6) Public health risk, 7) Psychic or physiological dependence liability, 8) If an immediate precursor of a controlled substance.

Controlled Substances Act (1970)

Established 5 classes -- “Schedules”-- of “narcotics and psychotropic drugs”

• Schedule I: no approved medical use in USA--e.g., heroin, marijuana, methaqualone, methamphetamine, LSD, psilocybin

- Schedule II – e.g., cocaine, pentobarbital, morphine, methadone, codeine
- Schedule III – e.g, ketamine, buprenorphine, Telazol (tiletamine & zolazepam)
- Schedule IV – e.g., diazepam, methohexital, phenobarbital, chloral hydrate
- Schedule V – e.g, pregabalin; preparations with specified small quantities of certain opiates (such as codeine)

Registration Requirements to obtain and use/dispense controlled substances

Business Categories of Registrants according to type of application

- Practitioners (e.g., MDs and veterinarians), Mid-level Practitioners (e.g., nurse practioners), Pharmacies, Hospitals/Clinics, and "Teaching institutions" (locations where medicine is taught but no clinical services are provided)
- Manufacturers, Import/Export, Distributors**, Researchers**, Dog Handlers, Labs
- Chemical: Manufacturers, Import/Export, Distributors
- Narcotic Treatment Clinics

Researcher Registrations

- Schedule I Researcher: A protocol must be submitted for each drug the registrant wishes to work with. The protocols are reviewed by the FDA.
- Schedules II-V Researcher: No specifications of drugs are required.
- Registrations must be renewed annually. Current cost: $244
- In some states (e.g., Maryland), state registration is required first.

Note: The legal relationship is between the DEA (and the state agency, if applicable) and the researcher registrant, not between the DEA and the university.

Can a Practitioner do research with controlled drugs using his/her registration?

- YES, as a “coincident activity.”

In this case, the rules that apply to “Researchers” on storage, record-keeping, etc. apply to that activity, not the rules that apply to the Practitioner handling of the drugs.

What are the “coincident activities” for a Researcher Registrant?

- Manufacture or import (specified compounds), conduct chemical analysis, and distribute compounds to other persons* authorized to conduct research

  *This clearly includes those working for/with the registrant (e.g., technicians, trainees, collaborators). Also can include distribution to another registrant if the proper paperwork is used (i.e., DEA form 222; copy of the registration).

- Instructional activities also may be carried out with Schedule II-V drugs.

Record-Keeping Requirements: Receipt and use of each lot received

- Receipt: Name of drug, Source, Date received, Manufacturer's lot number, Amount received (such that total amount of drug is clear: e.g., for liquids: 10 2-ml vials, 5 mg/ml; e.g., for powder: 2 10-gram bottles)
- Use: Date, Number of units removed, Amount remaining, Purpose, Name or initials of person removing that amount of drug
- Inventory: For Schedules I and II, add each shipment to the Inventory for that Schedule. The requirement to conduct inventories of Schedule I and II drugs every 2 years does not apply to preclinical research under the CSA.

Storage Requirements

- Stored controlled substances “shall be accessible only to an absolute minimum number of specifically authorized employees” (21CFR1301.72) as determined by the registrant.
- The registration application will have specified the means by which the registrant will assure secure storage.
- Security requirements vary based on Schedule, quantity, location (e.g., lab vs. clinic), adequacy of key control and/or combination locks, extent of unsupervised public access, and availability of security personnel.

Security Requirements, continued

- Research laboratories at universities may already be considered relatively secure given that they are not in areas frequented by the general public and have access restricted to employees per se.
- For laboratories that work with animals, the building security already may be substantial: e.g., not open to the general public, security guards, card-key access, restricted distribution of room keys. Thus, locked drawer or cabinet within the room itself may be sufficient.
- NOTE: Expired drugs still must be securely stored and under the control of the registrant. They still are considered subject to abuse.

Disposal Methodologies for Non-Practitioners

- September, 2014, DEA issued a final rule regarding disposal of controlled substances that has simplified requirements for animal researchers [21 CFR 1317.10(b) “non-practitioner inventory”; 1317.90].
- This voids the requirement to use “reverse distributors,” an approach that is not realistic for preclinical researchers.
- Substances must be rendered “non-retrievable.” That is, “unavailable and unusable for all practical purposes.” e.g., squirted onto a paper towel that goes into biohazard bag; poured into animal waste; down the drain, except . . . .
- Record destruction of small amounts in the record of use of that lot. Destruction of unopened vials should be recorded on DEA Form 41 with two witnesses.

Can the Attending Veterinarian prescribe controlled substances for research animals?

- This is possible for clinical purposes under the veterinarian's practitioner registration.
- For a large institution, the AV may choose not to go this route or only do so on a limited basis.

Relation of CSA Regs to AWA Regs and PHS Policy (the *Guide*)

Almost none (?)

- AWA and PHS Policy focus on the formulations that are preferred (i.e., "pharmaceutical grade"/commercial clinical use formulations) and use before expiration dates, which are not relevant to the CSA mandate to prevent drug diversion.

- In the chapter on "Veterinary Care," The *Guide* states that all "must comply with federal laws and regulations regarding human and veterinary drugs and treatments. Drug records and storage procedures should be reviewed during facility inspections." (p. 115)

Approaches to requesting changes in regulations or policy guidance for the CSA

- Request issuance of a "Significant Guidance Document" for preclinical researchers from DEA Headquarters Office of Diversion Control.
  - For example: Changing renewal period for researchers to 3 years (at lower overall cost) ? -- This is apparently already permitted under the Act itself.
- Formal petition for rule-making to DEA/Department of Justice itself under the Administrative Procedure Act (e.g., through AAMC?).
  - "e) Each agency shall give an interested person the right to petition for the issuance, amendment, or repeal of a rule."