NON-PHARMACEUTICAL GRADE SUBSTANCES / CONTROLLED SUBSTANCES MANAGEMENT
Non-Pharmaceutical Grade Substances (p.31 Guide)

- Use of Non-Pharmaceutical-Grade Chemicals and Other Substances. The use of pharmaceutical-grade chemicals and other substances ensures that toxic or unwanted side effects are not introduced into studies conducted with experimental animals. They should therefore be used, when available, for all animal-related procedures (USDA 1997b). The use of non-pharmaceutical-grade chemicals or substances should be described and justified in the animal use protocol and be approved by the IACUC (Wolff et al. 2003); for example, the use of a non-pharmaceutical-grade chemical or substance may be necessary to meet the scientific goals of a project or when a veterinary or human pharmaceutical-grade product is unavailable. In such instances, consideration should be given to the grade, purity, sterility, pH, pyrogenicity, osmolality, stability, site and route of administration, formulation, compatibility, and pharmacokinetics of the chemical or substance to be administered, as well as animal welfare and scientific issues relating to its use (NIH 2008).
Pharmaceutical Grade Substances

**Pharmaceutical grade compound:** A substance which is approved by the FDA (Green Book), or for which a chemical purity standard has been written/established by USP/NF, BP, Ph.Eur and is manufactured by these standards:

◊ **FDA Green Book:** The Generic Animal Drug and Patent Restoration Act requires that each sponsor of an approved animal drug submit to the FDA certain information regarding patents held for the animal drug or its method of use.

◊ **USP (United States Pharmacopeia):** A substance which has been approved by the United States Pharmacopeia Convention through evaluation of the participant’s quality systems using an audit of each manufacturing site for compliance with good manufacturing practices. The National Formulary (NF) is the official publication of the USP Convention, and contains two separate compendia – the USP and the NF.

◊ **BP (British Pharmacopoeia):** The British Pharmacopoeia (BP) is the official, authoritative collection of standards for United Kingdom (UK) medicinal substances for human and veterinary use.

◊ **Ph. Eur. (European Pharmacopoeia):** The European Pharmacopoeia defines requirements for the qualitative and quantitative composition of medicines, the tests to be carried out on medicines and on substances and materials used in their production.
When MUST you use Pharmaceutical Grade?

- When compounds are used for the clinical treatment of animals or to prevent or reduce/eliminate animal pain or distress PGCs must be used
- When compounds are used to accomplish the scientific aims of the study PGCs are required if available and suitable

The use of Non-PGCs in laboratory animals must be described and justified in the animal use protocol

AAALAC states that the investigator and the ACUC should consider the following factors for Non-PGCs:

- The provided scientific justification such as:
  - A PGC is not available; this includes new investigational compounds.
  - A PGC is not available in the appropriate concentration or formulation or the appropriate vehicle
  - The Non-PGC is required as part of an ongoing study or to compare to previous work

- Whether the chemical properties of the compound are appropriate for the study
- The method of preparation, labeling, administration and storage of formulations
- Compliant with applicable national/regional regulatory guidelines and relevant funding agencies.
Use of NPG Substances

The NIH Office of Laboratory Animal Welfare (OLAW) and the United States Department of Agriculture (USDA) have determined that the use of non-pharmaceutical-grade substances should be based on:

(1) Scientific necessity
(2) Non-availability of an acceptable veterinary or human pharmaceutical-grade compound
(3) Specific review and approval by the IACUC.

Other specific regulatory considerations include:

A. Cost savings alone is not considered an adequate justification for the use of non-pharmaceutical-grade substances.

B. While the possible implications of the use of non-pharmaceutical grade substances in non-survival studies appears less evident, the scientific issues remain the same and professional judgment, as outlined above, must still apply.

C. The consideration for non-pharmaceutical substance use pertains to all components, both active and inactive, contained in the preparation to be administered. Therefore, vehicles or diluents are as important a consideration as the active compound in the preparation.
CONDITIONS WHERE NON-PHARMACEUTICAL GRADE PRODUCTS MAY BE APPROVED: The IACUC may review & approve the use of nonpharmaceutical-grade substances in the following situations:

1. If no pharmaceutical grade drug is available for use, then other grades may be considered, and if scientifically justified, may be approved by the IACUC. If the vehicle or diluent is not pharmaceutical grade, this also must be justified.

2. Although an equivalent veterinary or human drug is available for experimental use, a different grade substance is required to replicate methods from previous studies because results are directly compared to those of previous studies.
Compounding

COMPOUNDING AGENTS: It is often necessary or desirable to dilute or mix agents prior to administration into a research animal.

- When diluting a pharmaceutical grade substance with a pharmaceutical grade diluent such as sterile water, the resulting mixture may be considered pharmaceutical grade.
- When diluting a pharmaceutical grade substance with a second pharmaceutical grade substance (e.g., ketamine with xylazine), the mixture is considered pharmaceutical grade product.
- When diluting a pharmaceutical grade compound with a non-pharmaceutical grade diluent such as olive oil, the resulting mixture would be considered non-pharmaceutical grade.
Non-Pharmaceutical Grade Substances

CAMPUS-WIDE EXCEPTIONS

• Avertin
• Pentobarbital

... the exorbitant cost of Nembutal (pentobarbital 50 mg/ml injection) has placed it logistically into the unavailable category

Non-Pharmaceutical Grade Substances

Discard Dates

- All chemicals used on or in animals must have a discard date clearly labeled on the container.
- Whenever possible, items should be compounded for the project the day of use and discarded immediately after use.
- Use manufacturer expiration date for non-compounded products.
- Sterile diluents and fluids without an manufacturer expiration date – up to 30 days after initial opening.
  
  DISCARD AFTER <insert the date 30 days in the future>
- Compounded drugs – up to 7 days after initial preparation.
  
  DISCARD AFTER <insert the date 7 days in the future>
WHAT IS A CONTROLLED SUBSTANCE?

- A specific, drug, chemical or immediate precursor regulated by the DEA due to its potential for abuse or addiction.

- Includes the salts, isomers, esters, and ethers of these chemicals.
WHO OVERSEES CONTROLLED SUBSTANCES?

- **U.S Drug Enforcement Administration (DEA)**
  - Established in 1973 under the US Department of Justice
  - Responsible for the enforcement of the *Controlled Substances Act of 1970*
    - The foundation for the body of regulations that governs the production, transfer, and disposal of controlled substances
    - Controlled Substances Act, Code of Federal or Substance Regulations (21 CFR, part 1300 to end).

- **North Carolina Department of Health and Human Services (DHHS):**
  - Controlled substances are also regulated at the state level
  - North Carolina Controlled Substances Statue (Chapter 90, Article 5),
  - North Carolina Administrative Code (10A; Sections 26E & 26F).
BACKGROUND

- Registration for use of controlled substances is an individual obligation!
- There is no statutory requirement for institutional management of controlled substance registration.
- Even so, Duke University has an interest in the health and well-being of its animals and regulatory compliance of its researchers, employees, faculty, and staff.
- The Office of Animal Welfare Assurance (OAWA) will assist controlled substance registrants by providing guidance and oversight, which will help assure compliance with all federal regulations, state rules, and institutional requirements.
AUDITS

- Site Audit: DHHS and/or DEA visit the storage site of the CS PRIOR to issuing a registration
- Schedule 1 Registrants: DEA performs an annual audit
- Spot Audit: DHHS or DEA RANDOMLY visit a Registrant to ensure compliance
DHHS and/or DEA Audits / Inspections (Duke Recommended Procedure)

- **PRIOR TO THE INSPECTION** (if possible): The Duke registrant applicant should contact OAWA for a pre-inspection assessment. OAWA will review and confirm the acceptability of the following:
  - A secured two-lock storage system for Controlled Substances.
  - Copy of the application for the DHHS Registration or the current DHHS registration.
  - b. Authorized user list
  - 3. A completed and signed 'Physical Inventory' form showing that there are NO Controlled Substances on site
  - 4. A ‘Purchase Log’ that will be empty (i.e., no controlled substances) but it should have all the other information completed
  - 5. A ‘Use Log’ that will be empty.

  Note: OAWA staff will perform the OAWA Pre-Inspection by assessing the conditions of storage and providing information or answering questions prior to the Site Inspection.

- **DURING THE INSPECTION:**
  
  The Registrant MUST be present. Additional staff may attend as well.

  At least one OAWA staff member should be invited to attend the inspection. The primary duties of the OAWA staff member will be to answer questions and address issues identified by the Agent.

- **AFTER THE INSPECTION:** OAWA and the Registrant will:
  
  Discuss any concern(s) identified, and
  
  Develop a corrective action plan for the concern(s)
ANNUAL REGISTRATION RENEWAL

- Both the state and the federal agencies require an annual renewal:
  - **DHHS Registration:** Individuals should receive a notice from the state in **September of each year** reminding them to renew the state registration. **October is the renewal month for all registrations in Durham County**, regardless of when in the calendar year the registration was initially granted.

  - **Federal Registration:** The federal registration is also annual, but is based upon the **calendar of the original federal registration (anniversary year)**. 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).
SECURITY FOR CONTROLLED SUBS.

- Controlled substances should be maintained behind a minimum of two (2) locks. Options for storage of the controlled substances are:
  - A locked container inside a locked cabinet.
    - The PREFERRED OPTION is for the locked container to be secured to an immovable surface such as a wall or shelf nailed in place.
  - A locked cabinet in a locked room.
    - The ‘locked room’ must always be locked when it is not occupied by either the registrant or an authorized user.

**NOTE:** In select circumstances, a securely affixed single locked device may be approved by the DHHS inspector.

**NOTE:** Drugs must be maintained at the registered location.
SECURITY FOR CONTROLLED SUBS.

- **Locks may be:**
  - Cipher locks (combination locks)
  - 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).
  - Both keys must be safeguarded and not accessible to unauthorized users.
STORING CONTROLLED SUBS.

- Generally, controlled substances should be stored in the containers in which they were shipped.
- In certain cases, changing the method of storage could impact the efficacy of the substance (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.
AUTHORIZED USERS

- **An Authorized User is an individual who has been approved by the registrant.**

- All Authorized Users must be approved personnel on a Duke IACUC Protocol.

- A list identifying the Authorized Users must be maintained inside the controlled substance file.
  - A copy of the suggested Authorized Users Form is available on the animal program web site.
  - Authorized Users must be included under Section A-3 of the applicable protocols. These additions may be made with a standard animal program Personnel Amendment form.
  - Registrants are responsible for all activities of the Authorized Users.
POWER OF ATTORNEY

- A Power of Attorney may:
  - Sign the DEA 222 form and receive Schedule II drugs in the absence of the registrant.
  - Perform other duties as the registrants representative (e.g. transfer, destruction of expired or excess controlled substances, etc.)
  - The registrant must submit all Power of Attorney requests to the Federal DEA.
  - A copy of the Power of Attorney should be provided to each distributor / vendor to allow controlled substances transactions.
Any written (paper) recording system may be used for maintaining controlled drug dispensing data.

- NOTE: Maintain inventories and records of controlled substances listed in Schedules I separately from all other records.

- NOTE: A 3-ring binder is recommended for maintaining controlled substance records.

- NOTE: Records must be kept onsite for at least 3 years. Scanning records to a secure server is a good idea.
RECORDKEEPING CONTROLLED SUBS.

- Recordkeeping must include:
  - Name of the substance (may be in page header)
  - Source of the substance (may be in page header)
  - Date of expiration of the substance (may be in page header)
  - Date of receipt (may be in page header)
  - Unique identification number for the bottle
  - Starting quantity of controlled substance
  - Date of use
  - Protocol (or project) for which it is being used
  - Animal (or group of animals) for which it is being used
  - Person dispensing the medication from storage
  - Person administering the medication to the animal(s)
  - Quantity (cc/ml/grams) of agent dispensed
  - Quantity remaining in the vial/bottle/box

- Suggestion: Use the forms on the animal program website – they capture these issues and items.
DISPOSING OF WASTE C. SUBS.

- The options include:
  - **Laboratory Disposal System:**
    - SMALL QUANTITIES (generally less than 0.5 ml)
    - Leftover from an experiment or procedure, an almost empty bottle, etc.
    - The registrant may dispose of the unneeded materials by one of the approved methods (to follow).
    - The registrant may request OAWA assist with disposal as described below.
DISPOSING OF WASTE C. SUBS.

- The options include:
  - **Animal Program Disposal System:**
    - The DHHS has authorized an individual in the Office of Animal Welfare Assurance to serve as the local Destruction Officer for moderate quantities of controlled substance, Schedules I - V.
    - The registrant (or authorized user) and the OAWA designee will complete the N.C. state controlled substance destruction form and the DEA 41 form to document the disposal; a copy of the form shall be maintained in the controlled substance documents of the registrant, in the animal program, server, and provided to the DHHS. Contact the Office of Animal Welfare Assurance for scheduling of controlled substance disposal.
    - **This should be limited to unopened bottles of expired CS or larger quantities of CS (> 50 mL)**
METHODS OF DISPOSING C. S.

- **Powders:**
  - Mix powders with liquid (e.g. Clorox or other disinfectant), pour onto absorbent material (e.g. soda-sorb, cat litter) and discard via the sharps container; or inject into a euthanized animal carcass and incinerate.

- **Liquids:**
  - Pour onto absorbent material (e.g. soda-sorb, cat litter) and discard via the sharps container; or inject into a euthanized animal carcass and incinerate.

- **Empty bottles:**
  - Remove the top of the bottle, rinse with water, dispose of the rinse water by pouring onto absorbent material (e.g. soda-sorb, cat litter) and discard bottle and absorbed material via the sharps container.
METHODS OF DISPOSING C. S.

- **Patches:**
  - Cut into small pieces and place the pieces in a sharps container.

- **Terminal amount in a syringe:**
  - Inject the substances onto absorbent material (e.g. soda-sorb, cat litter) and discard via the sharps container; or inject into a euthanized animal carcass and incinerate.

**SPECIAL NOTE:** **DO NOT DISPOSE DOWN THE SINK DRAIN.** CONTROLLED SUBSTANCES CONTAMINATE THE ENVIRONMENT!!!
The options include:

- **Reverse Distributor Disposal System:**
  - ALL QUANTITIES
  - When the Animal Laboratory Disposal System or the Program Disposal System is not the proper route of disposal (e.g., large quantities of controlled substances)
  - 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:
    - Pharmaceutical Dimensions – (336) 664-5287
DOCUMENTING DISPOSAL OF C. S.

- The individual disposing of the substance must sign the disposal log book.
- The witness must sign the disposal log book.
- Entries in the disposal log must include:
  - Name of controlled substance
  - Date and time it was disposed
  - Quantity disposed
  - Method of disposal
  - Initials of individual disposing of the agent
  - Initials of the witness observing the disposal

NOTE: Neither DLAR, OAWA, nor OESO will accept empty bottles or controlled substance for return or disposal.
AUDITING CONTROLLED SUBSTANCES

- **Laboratory Auditing of Controlled Substances:**
  - **Quarterly:**
    - The animal program recommends the registrant (or their designee) perform an audit of their controlled substance cabinet and the records.
    - At the conclusion of the audit, write in the next open line of the tracking log: “Audited on <date> by <print name> and found to be accurate (or define discrepancies). <sign name>”
  - **Semiannually:**
    - OAWA, DLAR, and/or IACUC will perform an audit of controlled substances as part of the semiannual program and facilities review.
    - At the conclusion of the audit, an auditor will write in the next open line of the tracking log: “Audited on <date> by <print name> and found to be accurate (or define discrepancies). <sign name>”
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!
REVISIONS OF C.S. REGISTRATION

- Both the NC state DHHS and federal DEA registrations must be modified:
  - The NC state DHHS registration should be revised first.
    - 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.

NOTE: 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.
REVISIONS OF C.S. REGISTRATION

- Both the NC state DHHS and federal DEA registrations must be modified:
  - The federal DEA registration should be revised once the DHHS approved modification has been received:
    - 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.
CANCELING C.S. REGISTRATION

- Cancellation requires the registrant:
  - Dispose of controlled substances as per this policy or transfer controlled substances to another approved registration.
  - Notify the DHHS to terminate their registration (Use Duke Letterhead).
  - Notify the DEA to terminate their registration.
    - Attach DEA certificate
    - Send any used DEA 222 forms (if applicable)

NOTE: Should the PI be relocating to continue their research at another location or institution, they can transfer their drugs from their Duke registration to their new registration at the other location once approved.

NOTE: Registration is not transferrable to another PI!
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