



ANIMAL TRACKS



A newsletter for the Duke research community

December 2007

<http://vetmed.duhs.duke.edu>

CONTROLLED SUBSTANCES MANAGEMENT PLAN CHANGES

Dear Colleagues:

In October we alerted you to significant changes in the use and management of controlled substances for the Duke animal program. These changes are required by North Carolina and United States Drug Enforcement Agency (NC DHHS and federal DEA). This issue of Animal Tracks is a reminder of the seriousness of the situation, and a plea for your immediate action if you presently use controlled substances for anesthesia or analgesia of your research animals.

Controlled substances are commonly used for animal anesthesia and pain relief, and for many studies, the absence of controlled substances will be the termination of animal studies since there are no acceptable alternatives. The Duke IACUC will not change the method of its review, and will continue to require the use of the most efficacious medication to ameliorate pain or distress in research animals. If the required medication is a controlled substance, and you do not have access to controlled substances, then you will not be able to proceed with your research goals. If you have not yet filed an application with the state of North Carolina (NC DHHS) or the federal government (DEA), then please initiate the process this week. Time is running out for functioning under the old system. After 1 February 2008, the new system will be in effect.

How will things change after 1 February?

- * No transfer (or purchase) of controlled substances from DLAR pharmacy without an active and approved state and federal license.
- * No purchase of controlled substances from non-DLAR sources (private vendors) without an active controlled substance license.

(See DEA on page 3)

SIGNS OF PAIN AND DISTRESS IN ANIMALS

Researchers and associates in our Duke research community are concerned about, and work diligently to prevent, pain or distress. The problem for most of us is recognizing the signs of pain or distress in animal. Animals express pain or distress using different behaviors than humans, and sometimes we miss what our animals are trying to tell us! Animals tend to 'hide' outward signs of pain, further complicating our ability to tell when they are suffering. Most of our research species hide signs of discomfort as long as possible. Knowing signs of pain in animals is critical to an pain management plan. Observing one or more signs of pain can tell us when our pain management plan needs enhancement!

Mice: After procedures which cause pain, mice may increase their sleeping times. Reduced food and water intake, with resultant weight loss, dehydration and wasting of the muscles on the back may be observed. Piloerection (erection of hair) and a hunched appearance can indicate pain or distress. The animal may fail to groom, but scratch more frequently. Sick mice are often isolated from the remainder of the group. Aggressive vocalization may be observed in the early stages, decreasing as pain or stress increases.

(See SIGNS on Page 2)

KEY SIGNS IN MICE

withdrawal, biting response, piloerection, hunched back, sunken eyes and abdomen, dehydration, weight loss, hypothermia.

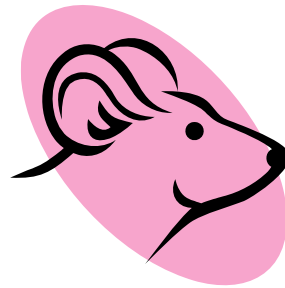
Upcoming Dates & Deadlines

January 3	Significant Change Meeting
January 7	New Protocol & Amendment Deadline
January 17	Significant Change Meeting
January 24	New Protocol Meeting
January 28	Amendment Deadline
February 4	New Protocol Deadline

CAN'T REMEMBER THE DATES FOR NEW PROTOCOLS?
JUST REMEMBER THAT NEW PROTOCOL DEADLINES
ARE 5 PM ON THE FIRST MONDAY OF EACH MONTH!

The eyes appear sunken, and ocular and nasal discharge may be noted as the animal's condition worsens. The respiration rate increases and breathing may be forced or labored. Defecation/urination are immediate reactions to stress in the mouse, and increase or decrease as stress continues. The movement of vibrissae (muscle hairs) becomes less evident as pain or stress continues. Affected mice become more timid and apprehensive; however, as pain or stress increases, they may become aggressive, with a tendency to bite. The animal may attempt to bite the source of pain or affected area, and may self-mutilate the affected part. Writhing movements are noted when the pain is abdominal. There is gradual assumption of a hunched, 'sleeping posture' away from any light source. Where limbs or feet are affected, sudden running movements are exhibited as an escape mechanism; there is increasing difficulty in maintaining posture. The mouse may show unsteady gait, difficulty in moving in straight line, and circling movements where balance is affected. Any of these may be the ONLY sign of pain you may notice, depending upon the nature of the study and the animal. Do not wait for all signs to be exhibited. In advanced pain or distress, the animal often becomes quiet and unresponsive, separates from the group and eventually becomes unaware of its surroundings. Hypothermia is observed with increasing deterioration in condition; the animal feels 'cold' to the touch.

Rats: Rats are generally docile and less aggressive than mice towards members of their own species and humans. Acute pain or distress is usually accompanied by constant vocalization and struggling. Rats will often lick or guard a painful area. Increased scratching can indicate chronic pain. A rat in pain may sit crouched with its head turned into its abdomen. Sleeping periods will be disturbed and increase if pain or distress are present. An elevated respiratory rate associated with sneezing occurs where the respiratory system is affected. Piloerection is noted, along with an increasingly untidy appearance as the animal fails to groom itself. There may be some hair loss. The animal ceases to eat and drink normally. There is poor skin tone, and evidence of muscle wasting along the back--indicative of dehydration and weight loss. During repeated painful or distressing procedures, animals may become more aggressive and resist handling, which will increase with increasing pain or distress. The eyelids rapidly assume a half-closed or almost-closed position. The eyes may appear sunken, and



ocular discharge is common, often progressing to red-colored hematuria exudate which may encircle the eye. Nasal discharge, if present, may be red-colored as well. Constipation or diarrhea may occur depending on the organ system(s) affected. Urination decreases with reduced water intake; however, frequency may increase where urinary infection or hormonal disturbance is present. Animals in pain initially show increased awareness/aggressive responses and a tendency to bite, but eventually become depressed and unresponsive. Exploratory behavior lessens. Aversive behavior is shown towards other animals. There is possible self-mutilation of affected parts in later stages. Abdominal contraction and stilted movements may occur if abdominal pain is present.

There may be increasing pain associated with locomotion. Lameness in one of the limbs or simply careful gait may be noted. A "waddling" gait occurs where abdominal enlargement take place as a result of intestinal obstruction or ascites. Circling often occurs where balance is disturbed. Initially, the rat exhibits increased angry or aggressive vocalization, especially on handling. There is a gradual reduction in vocal response as the pain or stress continues, and movement ceases unless a sudden painful stimulus is experienced. Hypothermia indicates significant deterioration in the animal's condition. A pale appearance indicates anemia or blood loss.

KEY SIGNS IN RATS

vocalization, struggling, licking, guarding, weight loss, piloerection, hunched position, hypothermia.

For more information on signs of pain and distress, one good place to look is the Canadian Council on Animal Care Guide, Volume 1 (2nd edition), 1993, Chapter X.

You can also visit the Duke Animal Program Web Site at http://vetmed.duhs.duke.edu/guidelines_for_signs_of_distress.htm for more discussion and examples of signs of pain or dis-

FBR On-Line AN INFORMATION RESOURCE FOR PUBLIC EDUCATION

Established in 1981, the Foundation for Biomedical Research (FBR) is the nation's oldest and largest organization dedicated to improving human and veterinary health by promoting public understanding and support for humane and responsible animal research. FBR is the leading voice of scientific reason and medical progress in the ongoing, sometimes violent debate that surrounds animal research. FBR has links for a wide variety of topics including: Animal Activism, Illegal Incidents Report, Quotes from Animal Extremists, DeBaKey Journalism Awards, Facts About Animal Research, Nobel Prizes Using Animals, Facts About Vaccines, and Public Opinions About Animal Research.

For more information visit the FBR web link:
<http://www.fbresearch.org/>

Questions & Answers on CONTROLLED SUBSTANCE USE IN THE DUKE ANIMAL PROGRAM

QUESTION: What is the DEA?

ANSWER: The DRUG ENFORCEMENT ADMINISTRATION (DEA) is the lead federal law enforcement agency responsible for enforcing the Controlled Substances Act (CSA). Established in 1973, DEA cooperates with other federal agencies, state, local, and foreign governments, private industry, professional groups, and other organizations to prevent unauthorized use of controlled substances. In North Carolina, the state DEA agency responsible for these activities is the North Carolina Department of Health and Human Services (NC DHHS).

QUESTION: I know what drugs I will need to use, but I do not know which schedule they fall under. Where can I find this information?

ANSWER: Drugs and drug products, i.e. controlled substances that come under the jurisdiction of the CONTROLLED SUBSTANCE ACT (CSA), are divided into five SCHEDULES, sometimes called CLASSES. Selected examples from each schedule are listed below. For a complete listing of controlled substances, see the Duke animal program web link 'Controlled Substance Schedules & 4 Digit Codes' located on the 'POLICIES' web page. The five schedules are based on the substance's medical use, potential for abuse, and safety or dependence liability:

Schedule I (CI) Substance: The controlled substances in this schedule are those that have no accepted medical use in the U.S., are not accepted as safe for use under medical supervision, and have a high abuse potential. Some examples are heroin, marijuana, LSD, peyote, mescaline, psilocybin, MDA, MDMA, ketobemidone, acetylmethadol, fenethylamine, tilidine, methaqualone, and certain fentanyl and meperidine analogs.

Schedule II (CII) Substances: The controlled substances in this schedule have a high abuse potential with severe psychological or physical dependence liability, but have accepted medical use in the U.S. CII controlled substances consist of certain narcotic, stimulant, and depressant drugs. Some examples of CII narcotics are: opium, morphine, codeine, hydro-morphone, methadone, meperidine (Demerol), cocaine, oxycodone (Percodan), anileridine (Lertine), morphine, and oxymorphone (Numorphan). Also in CII are the stimulants amphetamine (Dexedrine), methamphetamine (Desoxyn), phenmetrazine (Preludine), and methylphenidate (Ritalin); the barbiturates (amobarbital, pentobarbital [Nembutal], secobarbital); fentanyl (Sublimaze), etorphine hydrochloride, and phencyclidine (PCP).

(See Q&A ... on page 4)

(DEA ... from page 1)

For those individuals with Duke hospital pharmacy 'rights,' controlled substances cannot be scripted out of the Duke hospital pharmacy for use in animals.

Since the application process involves both state and federal agencies, please plan on 4-6 weeks for receipt of the license (which means you need to apply immediately if you plan on using controlled substances for anesthesia or analgesia after 1 February 2008).

Wishing you a productive research month and a pleasant holiday season,

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Schedule III (CIII) Substances: The controlled substances in this schedule have an abuse potential and dependence liability less than those in CI and CII, and have an accepted medical use in the U.S. They include preparations containing limited quantities of certain narcotic drugs, and other nonnarcotic drugs such as: derivatives of barbituric acid (thiopental), except those that are listed in another schedule, glutethimide (Doriden), buprenorphine, methyprylon (Noludar), nalorphine, benzphetamine, chlorphentermine, clortermine, phendimetrazine, ketamine, or ethansol.

Schedule IV (CIV) Substances: The controlled substances in this schedule have an abuse potential and dependence liability less than those listed in CIII and have an accepted medical use in the U.S. They include such drugs as: barbital, phenobarbital, methylphenobarbital, chloral hydrate, ethchlorvynol (Placidyl), ethinamate, (Valmid), paraldehyde, methohexital, fenfluramine, diethylpropion, phentermine, chlordiazepoxide (Librium), diazepam (Valium), oxazepam (Serax), clorazepate (Tranxene), flurazepam (Dalmane), lorazepam (Ativan), alprazolam (Xanax), temazepam (Restoril), triazolam (Halcion), mebutamate, dextropropoxyphene (Darvon), and petazocine (Talwin).

Schedule V (CV) Substances: The controlled substances in this schedule have an abuse potential and dependence liability less than those listed in CIV and have an accepted medical use in the U.S. They are often available without prescription, and include preparations containing limited quantities of certain narcotic drugs generally for antitussive and antidiarrheal purpose.

QUESTION: I already have a DEA license issued by the federal government. Do I need a NC state license also?

ANSWER: While licenses are person specific, they are also location specific! The license was initially granted based upon a specific controlled substance storage process and storage location. If you move, say from California to North Carolina, your old license shows the location as California, the new location has not been approved. You may be able to purchase controlled substances based upon your old license, but this is not acceptable. According to the NC DHHS instructions, a NC state license is **REQUIRED** to use controlled substances in North Carolina. If a researcher had a federal DEA license when moving to North Carolina, they should submit NC DHHS Form 225 to obtain a NC license prior to working with animals. The researchers should also notify the federal DEA of their location change too.

QUESTION: I have a practitioner license for my clinical duties with human patients. Can I use this license for my research work with animals?

ANSWER: No. A practitioner license does not confer approval for use of controlled substances with animals (except for veterinarian's wherein clinical use is for an animal patient). The PRACTITIONER LICENSE is obtained under DEA form 224. The RESEARCHER LICENSE is obtained using DEA form 225. A practitioner license is for clinical use of controlled substances in humans (for physicians) or animals (for veterinarians). Practitioner licenses are **NOT** for research purposes.

QUESTION: If I only use ketamine, should I get a license only for schedule III?

ANSWER: When applying for the license, researchers should select the schedule of medications that will be used. If ketamine is the **ONLY** agent that will be used in a research, then Schedule III could be the category selected. It costs no more, and might be a wise consideration, to list those agents that would be useful in the research activity, even though the agents are not being used presently.

QUESTION: Can other investigators use my individual DEA license, as long as those individuals are listed on the approved animal protocol?

ANSWER: North Carolina DHHS have agreed that small groups of individuals may use a single DEA license for controlled substances in animals. The individual holding the license will be accountable for all controlled substance use from the controlled substance cabinet. The best recommendation for the license holder is to keep a memo in the controlled substance cabinet identifying who has access to the controlled substances. It is important that individuals using controlled substances in animals **MUST** be on the IACUC approved animal protocol.

QUESTION: We perform research in two different buildings on campus. Do I need two separate licenses or can one license be extended over two locations?

ANSWER: This question addresses the potential for a 'satellite storage location.' The decision on whether the second location will require separate licensure will be made by the NC DHHS agent during the application inspection process. As a general statement, state and federal DEA licenses are based upon storage at a specific geographic location, which includes the security processes for that location and the substances stored at that location. If one keeps a 'satellite pharmacy,' there must be sufficient measures in place at the satellite to assure consistent management and control of the substances. 'Satellite pharmacies' for researcher licenses may require a second license.

QUESTION: What security measures are required to hold controlled substances in my laboratory?

ANSWER: The general security requirements set forth in the Code of Federal Regulations (CFR) require all registrants and applicants for registration to provide effective physical security controls and operating procedures to guard against theft and diversion of controlled substances. Substantial compliance with these requirements and standards set forth in Title 21 CFR Sections 1301.72-1301.76 may be deemed sufficient by DEA after evaluation of the overall security system and needs of the individual applicant or registrant considering the following factors:

1. Type of activity conducted (e.g., formulation of drugs versus small vial research use).
2. Type and form of controlled substances (e.g., bulk liquids or dosage units, usable powders or non-usable powders, etc.).
3. Quantity of controlled substances.
4. Location of premises/security needs (e.g., high vs. low crime areas, adjacent/attached buildings, etc.).
5. Type of building construction/general characteristics (e.g., metal curtain, wood frame, masonry, number and type of doors, windows and other openings, etc.).
6. Types of secure enclosures (e.g., modular vaults, thin metal storage containers, etc.).
7. Type of closure (e.g., built-in combination locks, key locks, padlocks, self closing, etc.).
8. Key and lock control (e.g., adequacy, accountability, routine changing, issuance and control procedures, logging, central repository, combination security, etc.).
9. Alarm systems (e.g., adequacy of supervision, testing, signal, etc.).
10. Public access/perimeter fencing (e.g., extent of unsupervised public access to the facility, etc.).
11. Supervision of employees (e.g., access control, identification, control of and accountability for identification, responsibilities of employees, etc.).
12. Guest/visitor procedures (e.g., access control, logging procedures, identification media, internal movement control, etc.).
13. Local police/security force (e.g., availability, frequency of patrol, etc.).
14. Adequacy of internal systems for monitoring controlled substances (e.g., storage security).

QUESTION: My present license is renewed every 3 years, but the NC DHHS instructions indicate an annual renewal is required. Please clarify.

ANSWER: The annual renewal requirement is for researcher licenses (state and federal). The practitioner license is a three year license.

QUESTION: Our drug cabinet is itself double-locked (an outer door and an inner door, with differing design locks and keys). Is that sufficient?

ANSWER: Yes. While there are exceptions to every rule, the description does meet the requirements for double locking devices. There is no requirement for a 'safe' or 'strong box' for storing controlled substances.

QUESTION: Do I need to display my controlled substance license?

ANSWER: No. Upon receipt of registration certificate, you should check all information for accuracy. Certificates SHOULD NOT be displayed. Certificates should be filed out of sight but remain at the registered location. Research registration certificates are geography specific. If a change of location occurs contact the N.C. Drug Control Unit and the federal DEA.

QUESTION: When can I file for a federal license?

ANSWER: When you satisfy the basic compliance with State regulations for security and accountability, a DHHS controlled substance registration number will be issued. At that time you may complete a federal DEA application. Federal DEA investigators usually do not conduct inspections, but rely upon the state inspections. Generally a valid DHHS controlled substance registration number (located on certificate) is sufficient to apply and receive a controlled substance registration from the federal DEA.

QUESTION: What should I do with the drugs I have on hand?

ANSWER: Use them in routine research activities as appropriate. Expired drugs awaiting disposal can be transferred to the DLAR pharmacy (except Schedule I agents). Any transfer of controlled substances from one researcher to another researcher requires that both researchers have a DEA licenses (state and federal) and the transfer is documented appropriately.

QUESTION: Is the NC DHHS inspection a physical inspection?

ANSWER: After each application is received, an inspector for the NC HHS will contact you to schedule an on-site inspection. A federal DEA controlled substance registration is not submitted until an applicant has been through the NC HHS inspection process. The NC DHHS has stated that if the applicant provides sufficient and clearly identified photographs of the controlled substance storage equipment when the initial application is filed, then the NC DHHS may elect to issue the state license without a physical inspection. This option will be considered as a means of easing the inspection process.

(Continued on the next page)

QUESTION: Must controlled drugs currently in the lab be entered into the OESO database or those just purchased after Feb 1, 2008?

ANSWER: The OESO is continuing to develop the web input pages, and we expect completion within a week or so. Beginning 1 Feb, ALL controlled substances on hand should be entered into the database. This database will be used locally to identify areas of use and who has oversight responsibility for that area and those controlled substances.

QUESTION: I see there is a licensing fee for the state and the federal license. How can I pay for the license fee? Who should pay the fee?

ANSWER: The licensing fee may be paid from departmental or personal funds, or in some cases grant funds (according to Duke Office of Research Administration, the license fee cannot be paid out of federal grants, but if approved by the sponsor, may be paid by non-federal grants). Both the state and the federal agencies prefer to be paid by credit card (but check is acceptable). You may either pay for the fees with your personal credit card or you may use the Duke issued Corporate Credit Card for license fee payment, and then IR the funds to the appropriate department account. The federal license can be paid by credit card on-line at their web site. When paying for the state license by credit card, FAX a copy of the DHHS form 225 with the credit card information below to Christina Baker @ FAX number 919.715.5214:

- * Visa or Mastercard
- * Credit card number
- * Expiration date on the card
- * Name on the card
- * Phone number of the card holder (just in case there is a problem)

QUESTION: Since this change in our process is required by the state and federal agencies, and the change requires the fee based licenses, can Duke researchers be exempted from paying the registration fee?

ANSWER: Title 21 of the Code of Federal Regulation, Section 1301.21 allows for exemption of federal (not state) DEA license fees for certain categories of individuals and institutions. Specifically, 'any hospital or other institution which is operated by an agency of the United States, of any State, or any political subdivision or agency thereof; or any individual practitioner who is required to obtain an individual registration in order to carry out his or her duties as an official of an agency of the United States, of any State, or any political subdivision or agency thereof.' Duke is a private institution and not under the provisions for exemptions of the state or federal fees. However, if you are faculty at the VA Medical Center, and if your supervisor at the VA will sign the application verifying your position at a federal institution, you can apply for an exemption to the federal fee of \$184.00 (for the original application and the renewal application).

QUESTION: What if we discover we need to add additional controlled substances to our license?

ANSWER: If additional controlled substances are needed (for a Duke protocol), submit an amendment to the approved protocol to the Duke IACUC. Also submit a letter to NC DHHS requesting the new agent be added to your license. Federal additions can be accomplished on their web site (on-line submission). If approved, then both agencies will forward a modified registration reflecting the appropriate schedule. Submitting another application will not be necessary. Both processes (IACUC review and state/federal review) can occur at the same time if desired, but no unlicensed substances may be purchased or used until IACUC approved, and state and federal licensed.

QUESTION: Do I submit a new application each year?

ANSWER: No. Complete NC DHHS and DEA form 227, in the same manner as you filed the original application (Form 225). Drug codes shall apply to controlled substances used for research at the time of application. Renewal applications are generally mailed to registrant between 45 and 60 days prior to expiration of your controlled substance registration certificate.

QUESTION: Should disposal of substances require a witness, or can the controlled substances cabinet registrant dispose of the substances on their own signature?

ANSWER: The regulations are not specific, but when posed with this question, the federal agent suggested the best approach was for the registrant to find a non-lab member to serve as a witness. In a pinch, any witness is acceptable if a non-lab witness is not available, and as long as it is clear that the witness did not have access to the controlled substances. If a lab member must be used (due to the time of day or other requirement), then the federal agent suggested that a non-laboratory member should conduct an audit to confirm the activities of the laboratory members, just as a second layer of assessment that the process used was appropriate. He ended by saying it was not a requirement, but for the best interest of the license holder and to keep everything 'above board,' an outside audit is recommended.

QUESTION: What is the appropriate method to dispose of controlled substances when one ampule has been opened (so it can't be placed back in the cabinet), but there is material remaining and will not be used in the research activity?

ANSWER: The remaining drug in the ampule can be placed in a sealed container, labeled, and returned to the controlled substance cabinet. Be sure and record the actions in the log. These actions should be witnessed (with signatures). If the agent can be used at a later date, that is ok. If the agent must be destroyed, then maintain it until it can be transferred to DLAR (if Schedule II - V), or via the 'Reverse Distributor' option, or until the state (NC DHHS) agent attends and records the destruction of the agent. If it is a Schedule I agent, the license holder must maintain ownership of the agent until it is sent to the 'Reverse Distributor.'



OAWA's Brown Bag Seminar

Friday, January 11th, 2007

Noon – 1 p.m.

Bryan Research Building: Room 103

Dr. Charles B. Clifford

Dir, Pathology and Technical Services

Charles River Laboratories, Inc

will be presenting:

Why Should I Care About Rodent Infectious Diseases Common in Animal Facilities?

Laboratory rodents interact with their microbial environment in complex ways. Although some organisms are beneficial, and commensal organisms may require little host response, primary and opportunistic pathogens may instigate a complex chain of host defense mechanisms which can result in variability in research results.

This presentation will focus on the interactions of common subclinical infections with the animals, as well as published reports of how these infections impact research outcomes. Shortcomings of some of the published reports will also be discussed.

You won't want to miss this talk! We are very fortunate to have this opportunity for an international expert to speak to us about critical research concerns.

The presentation will be on **January 11th, 2007** in room **103 of the Bryan Research Building**, located at 421 Research Drive, on Duke University's West Campus.

Attendees are encouraged to bring a lunch. OAWA will provide drinks and desserts. The session will begin promptly at noon. Please arrive early to sign-in and find a seat.

For those who will be coming from off campus, driving directions and parking information can be found at the following link: <http://neuro.duke.edu/Links/map.htm>

This session will count for 1 CEU of AALAS In-house Training Credit