A3294-2F

POLICY

It is the policy of this institution and the responsibility of the UNMC/UNO IACUC to mandate proper management for the procurement, use, documentation, and storage of all controlled and non-controlled drugs used in research animals. All drugs must be stored, labeled, and disposed of according to the procedures outlined in this policy.

In addition, the Drug Enforcement Agency (DEA) requires physicians and research personnel who administer controlled substances to maintain records of drugs purchased, distributed and dispensed. The IACUC, and ultimately, the DEA shall have access to all records pertaining to controlled substances for inspection and/or copy.

REGULATIONS

DEA, This document which adheres to Title 21 United States Code (USC) Controlled Substances Act https://www.dea.gov/druginfo/csa.shtml
Title 21, CFR Section 1301.71(a), requires that all registrants provide effective controls and procedures to guard against theft and diversion of controlled substances.

USDA APHIS/AC Policy 3 the use of expired materials such as pharmaceuticals "on regulated animals is not considered to be acceptable veterinary practice and is not consistent with adequate veterinary care as required by the regulations promulgated under the Animal Welfare Act.

PROCEDURES

1.0 EXPIRED DRUGS

1.1 The use of expired drugs is not considered to be acceptable veterinary practice. Please refer to Policy for Expired Drugs or Medical Materials for more complete information.

2.0 PHARMACEUTICAL GRADE DRUGS/REAGENTS

2.1 Only pharmaceutical grade drugs (includes reagents, compounds, diluents, fluids) should be used on animals in research or instruction unless otherwise justified, reviewed, and approved by the IACUC. Please refer to Policy for Non-Pharmaceutical Grade Compound Use in Animals for more complete information.

3.0 DRUG/CHEMICAL COMPOUND PROCUREMENT, STORAGE, AND INVENTORY (See Section 6.0 for Controlled Drugs)

3.1 Upon ordering, receipt, and administration of drugs/chemical compounds intended for use in research animals written documentation must be available to confirm that the correct drug and concentration of the drug in the correct formulation was received.

3.2 Below are examples of the information that should be documented depending on the drug type.

A. Medications approved for use in animals such as anesthetics, analgesics, antibiotics, etc.:

1) Drug Name
2) Concentration
3) Quantity/Amount Received
4) Date and initials of Person(s) that Ordered and Received the Drug
5) All receipts and drug information received from company

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B. Non-pharmaceutical drugs/chemical compounds not intended for animal use but approved in the IACUC protocol.
  1) Chemical Name
  2) CAS Number
  3) Formula Weight
  4) Quantity/Amount Received
  5) Date and initials of Person(s) that Ordered and Received the Drug
  6) All receipts and drug information received from company

C. All drug order and receipt information is subject to review by the IACUC, CM, or PAL at any time.

3.3 All drugs should be kept in a secure area.
  A. Drugs to be used on research animals must be stored in a separate location from other chemicals used for non-animal related research projects.
  B. Do not store controlled and uncontrolled drugs in the same primary storage container.
  C. Limit the number of personnel who have access to secured drugs.

3.4 A system to minimize the amount of drug kept in inventory to avoid drugs expiring is recommended and may include the following:
  A. Storing drugs in one location.
  B. Performing monthly checks of your inventory to identify expiring drugs.
  C. Documentation of person performing scheduled inventory checks.
  D. All expired drugs and medical materials must be clearly labeled "EXPIRED" prior to disposal or pickup.

4.0 MIXING AND/OR LABELING ALL DRUGS/CHEMICAL COMPOUNDS

4.1 When drugs/chemical compounds are made into solutions/cocktails to be given to animals' sterile diluents must be used and/or an approved method of sterilization is to be followed according to the policy for non-pharmaceutical grade drugs and the approved IACUC protocol.

4.2 You must label all secondary drug containers and/or syringes with the following information:
  A. Drug name
  B. Drug concentration
  C. Expiration date
  D. Preparation/Mixture Date (non-pharmaceutical grade drugs)

4.3 If mixing drugs you must label all drugs that are in the cocktail

4.4 The expiration date of the drug or diluent/vehicle in a cocktail that expires first must be written on the secondary container, and any unused portion of the cocktail must be disposed of by this date.

4.5 Non-pharmaceutical grade drugs require a mix date and an expiration date
  A. The expiration date of the diluent used must be on the secondary container
  B. Because of recommendations for different chemical grade drugs, a mix date must also be on the container
    1) Examples include: 1) Tribromoethanol (Avertin) is not recommended to be used after 14 days from the date it is mixed; 2) Urethane/chloralose is not recommended to be used after 30 days from the date it is mixed

5.0 DISCARDING EXPIRED or UNUSED DRUGS (*See Controlled Drug Section 6.5 for additional instructions)*

A. Label all expired drugs "Expired" and store in a secure location segregated from other drugs being used on animals.
  1) Do **not** pour drugs/chemicals/compounds down the sink or into any other drain that flows into sewer.
  2) Do **not** dispose of drugs/chemicals/compounds into trash.

B. Contact the UNMC Environmental Health and Safety (EHS) or UNO Chemical Safety Office for detailed instructions on proper disposal and/or surrender of expired drugs.
  1) UNMC EHS **http://www.unmc.edu/ehs/** (formerly Chemical and Radiation Safety) (b) (6) (b) (6)

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2) UNO Chemical Safety (b) (6)

6.0 CONTROLLED DRUGS

6.1 A controlled (scheduled) drug is one whose use and distribution is tightly controlled because of its abuse potential or risk.

6.2 Controlled drugs are rated in the order of their abuse risk and placed in Schedules by the DEA.
- **A.** The drugs with the highest abuse potential are placed in Schedule I, and those with the lowest abuse potential are in Schedule V.
- **B.** These schedules are commonly shown as C-I, C-II, C-III, C-IV, and C-V.

6.3 Drug Disposition Records/Usage Logs must be maintained for all controlled drugs.
- **A.** Inventory records must be retained for a minimum of two years according to DEA 21CFR.
  - **1)** After the initial inventory is taken, the registrant shall take a new inventory of all stocks of controlled substances on hand at least every two years. The biennial inventory may be taken on any date which is within two years of the previous biennial inventory date.
- **B.** A Drug Disposition Record is required for each controlled drug on hand and must document the **receipt**, **administration**, and **disposal** of each of those drugs.
- **C.** For each drug, the disposition record must reflect the **total volume of drug on hand**. (e.g. 10 – 10 ml. bottles of Ketamine = 100 mls.) For each use deduct from the total volume on hand.
- **D.** A witness should be present and initial the log to attest that the drug was legitimately disposed of.
- **E.** You may contact the IACUC office or Comparative Medicine to request the recommended Controlled Drug Disposition Record, or you may develop your own form.

6.4 Proper Storage of Controlled Drugs
- **A.** Controlled Drugs should be stored under Double Lock and Key separate from other (uncontrolled/unscheduled) drugs.
- **B.** Store in a **double lock safe** constructed of tamper proof material. Options Include:
  - **1)** Store in a **locked box** in a **locked drawer**, with the keys stored out of site.
  - **2)** Store in a **locked drawer** in a **lab or office that remains locked** at all times when not occupied, with keys stored out of site. *(The 'locked room' must always be locked when it is not occupied by either the registrant or authorized user.)*
- **C.** Controlled Drugs should be stored in the physical location registered with the DEA.
  - **1)** Drugs may be removed for up to 24 hours from the registered storage location for use in facilities and treatment rooms. (For more information about the registered storage locations on file please contact the DEA.)

6.5 Disposal of expired or unused stock of controlled drugs:
- **A.** Expired drugs must be disposed of by qualified individuals after being rendered "non-retrievable".
- **B.** Label all expired drugs "Expired" and store in a secure location segregated from other drugs being used on animals. Note: Expired controlled drugs must be secured under double lock.
  - **1)** Do **not** pour drugs/chemicals/compounds down the sink or into any other drain that flows into sewer.
  - **2)** Do **not** dispose of drugs/chemicals/compounds into trash.
- **C.** Contact the UNMC Environmental Health and Safety (EHS) or UNO Chemical Safety Office for detailed instructions on proper disposal and/or surrender of expired drugs.
  - **1)** UNMC EHS **http://www.unmc.edu/ehs/** (formerly Chemical and Radiation Safety) (b) (6) (b) (6)
  - **2)** UNO Chemical Safety (b) (6)
- **D.** Complete DEA form 41 and maintain with controlled drug records.
  - **1)** For more information about controlled drug disposal contact the DEA Drug Disposal Information.

6.6 Registration procedures for Nebraska follow federal regulations as indicated below.
- **A.** New applicants, who do not currently possess a DEA license to conduct business with controlled substances in the following categories must apply using Form 225 and 225a for renewal:

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1) Manufacturer
2) Distributor
3) **Researcher -** *Exemption from application fee applies to federal, state, or local government official or institution. The applicant's superior or agency officer must certify exempt status. The signature, authority title, and telephone number of the certifying official must be provided. The address of the fee exempt institution must appear in Section 1.*
4) *On line application forms are available at; http://www.deadiversion.usdoj.gov/drugreg/index.html#1*
5) Analytical Laboratory
6) Importer
7) Exporter

6.7 For Information on obtaining forms and assistance please contact the following field office for Nebraska:

A. KANSAS CITY DISTRICT OFFICE
7600 College Blvd., Suite 100
Overland Park, KS 66210

1) Diversion Number: (913) 951-4100
2) Diversion Fax: (913) 951-3684
3) Jurisdiction: Kansas, Nebraska and Western Missouri KANSAS CITY DISTRICT

6.8 Registration Contact Numbers

A. Serving Iowa, Kansas, Missouri, Nebraska, South Dakota and Southern Illinois - (888) 803-1179 or (314) 538-4622 (Fax)

6.9 For Additional Information Please See the Office of Diversion Control Website.

A. Practitioners Manual ***http://www.deadiversion.usdoj.gov/pubs/manuals/pract/index.html***

LINKS TO RELATED FORMS, RECORD LOGS, AND SOPS

Controlled Drug Disposition Record
DEA Form 41

Biennial Controlled Substance Inventory

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POLICY

Pharmaceutical-grade agents are to be used whenever they are available, even in acute procedures. The use of non-pharmaceutical grade agents in laboratory animals under certain circumstances may be a necessary and acceptable component of biomedical research.

In the event that a non-pharmaceutical grade agent has to be used due to (1) scientific necessity and/or (2) non-availability of a veterinary or human pharmaceutical grade compound, specific review and approval by the IACUC is required. Cost savings alone is not an adequate justification for using non-pharmaceutical grade agents.

In addition to strong justification for the need to use non-pharmaceutical grade agents, the method of preparation of the drug, means to ensure sterility and biocompatibility, and storage conditions must be described in the IACUC protocol. In particular, it is expected that the procedures and criteria described in this policy are followed when preparing and storing agents intended for administration to animals. Exceptions may be granted for compounding of the final preparation used for oral gavage or administered in food or drinking water.

Definitions:

- Pharmaceutical grade agents: A drug, biologic, reagent etc. which is approved by the Food and Drug Administration (FDA) or for which a chemical purity standard has been written/established by United States Pharmacopeia (USP), National Formulary (NF), European Pharmacopeia (Ph. Eur), or British Pharmacopeia (BP).

REGULATION

Reference 9CFR Animal Health and Husbandry Standards, 3.110 Veterinary Care, USDA Animal Care Resource Guide Policies, March 25, 2011, Policy #3 Veterinary Care:
Investigators are expected to use pharmaceutical-grade medications whenever they are available, even in acute procedures. Non-pharmaceutical-grade chemical compounds should only be used in regulated animals after specific review and approval by the IACUC for reasons such as scientific necessity or non-availability of an acceptable veterinary or human pharmaceutical-grade product. Cost savings is not a justification for using non-pharmaceutical grade compounds in regulated animals.

Guide for the Care of and Use of Laboratory Animals, ILAR, NAS, Eighth Edition 2011, pg 31: 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).

PROCEDURE

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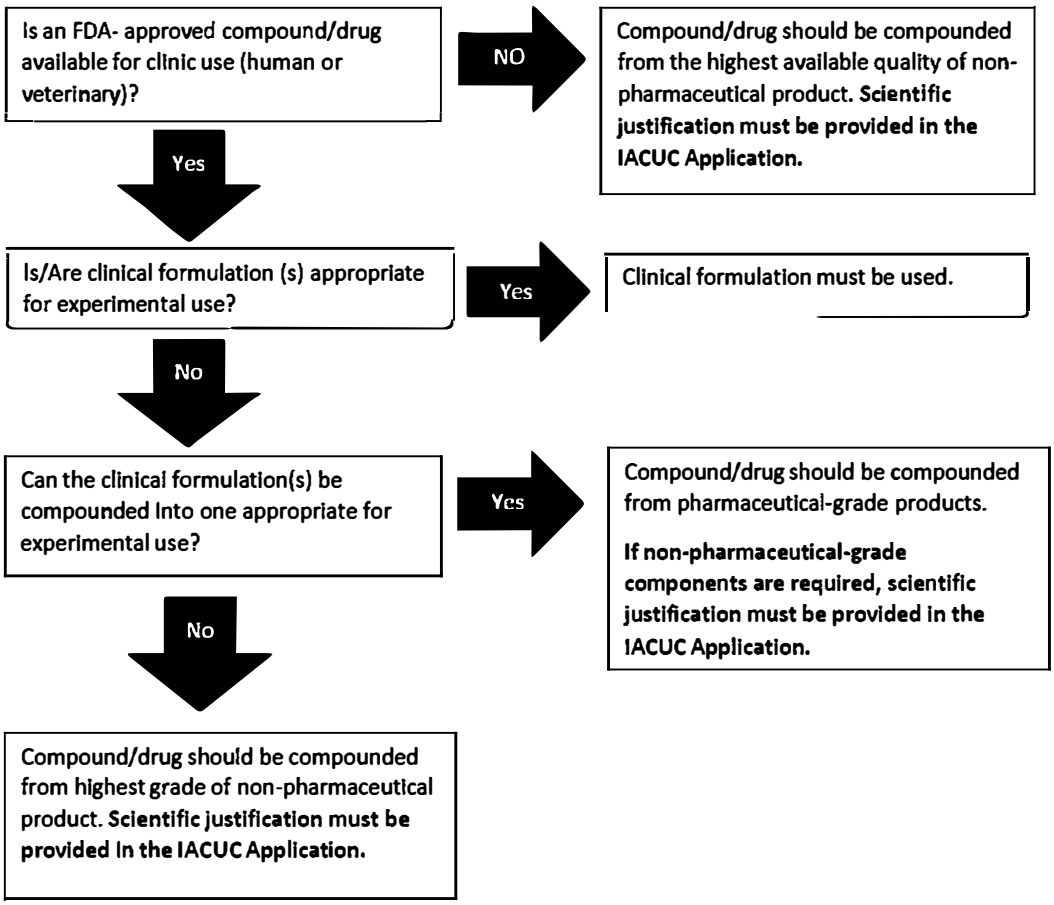
1.0 The following questions should be considered when deciding what formulation of agent to use:



2.0 When developing and reviewing a proposal to use non-pharmaceutical grade agents and/or investigational drugs where the grade and formulation is not known the Investigator and the IACUC should consider the following:

2.1 Animal welfare and scientific issues related to the use of the agent(s).

2.2 Potential for contamination, safety, efficacy, and the introduction of research variables.

3.0 For all agents, the Investigator and the IACUC should consider the following:

3.1 The grade of the chemical being proposed (i.e. how pure the agent is).

- **A.C.S.** - A chemical grade of highest purity and meets or exceeds purity standards set by American Chemical Society (ACS).
- **Reagent** - High purity generally equal to A.C.S. grade and suitable for use in many laboratory and analytical applications.
- **Lab** - A chemical grade of relatively high quality with exact levels of impurities unknown; usually pure enough for educational applications. Not pure enough to be offered for food, drug, or medicinal use of any kind.
- **Purified** - Also called pure or practical grade, and indicates good quality chemicals meeting no official standard; can be used in most cases for educational applications. Not pure enough to be offered for food, drug, or medicinal use of any kind.
- **Technical** - Good quality chemical grade used for commercial and industrial purposes.

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Not pure enough to be offered for food, drug, or medicinal use of any kind.

3.2 Issues related to sterility, pyrogenicity, stability, pH, osmolality, site/route of administration, pharmacokinetics, physiological compatibility, and quality control.

3.3 The formulation of the final product.

4.0 Reconstituting or diluting agents to be administered to animals.

4.1 When reconstituting or diluting agents to be administered to animals, it must be performed in a clean/sanitary environment with a method to sterilize the final preparation.
- Clean/sanitary work space (Safety cabinet or chemical fume hood when required)
- Disposable latex or nitrile gloves
- Sterile diluent/vehicle/solvent
- Sterile syringes
- Sterile storage containers/vials with stoppers that provide elastomeric closure to prevent pathogen entry are required for injectables.
- For agents to be administered orally ensure that they are stored in containers that prevent microbial contamination.

4.2 Where possible agents and diluents/vehicles/solvents should be passed through a syringe filter (0.22 um or finer).
- This can be done when transferring to a sterile injection vial/container.
- If there is any question about the sterility of a stored solution, it should also be filtered at the time of use.
- If filtering is not possible (e.g., nanoparticles) alternative methods of sterilization must be described or justification of the need to use non-sterile agent must be provided.

4.3 Diluents/vehicles/solvents must be specified in the animal use protocol. The diluent/vehicle solvent will be evaluated based on toxicity to animals, compatibility with agents, and volume/route of administration.
- See a list of common diluents/vehicles/solvents in Section 4.11.

4.4 The pH of the final preparation must be checked and should be between pH 4.5 and 8.0.
- Use of a solution with a pH outside this range must be reviewed by the IACUC and may not be approved if considered potentially toxic and/or painful to the animal.

4.5 The Osmolality of the final preparation should be isotonic, (around 300 mOsm/kg) whenever possible.
- Non-isotonic formulations may either cause red blood cell crenation or haemolysis when administered via the intravenous route, or may cause localized tissue damage and associated pain upon injection.
- Non-isotonic formulations should be administered slowly and in small volume.

4.6 Storage container/vials must be labeled with the agent, concentration, and expiration date and mix date.
- When no expiration date is available, mix date is required and length of time that agent can be maintained must be based on known efficacy.

4.7 Prepare only as much as can be used in a reasonable period of time.
- Agents must be stored properly with consideration for chemical properties and according to manufacturer or similar commercial product recommendations. (e.g., freezer, refrigerator, etc.).
- Agents must not be used if they are cloudy, discolored, precipitated, etc.

4.8 You should keep a written record of preparation of agents and administration of final preparation to animals.

4.9 Some agents may have been tested for pyrogens, such as endotoxins. Check the source of the agent for information to see if pyrogen testing has been performed.
- Pyrogens, such as endotoxins may cause fever when injected into an animal.
- Sterility does not assure that pyrogens are not present.

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- Filtering does not remove pyrogens.
- Pyrogen testing is not practical for small lots of prepared agent.
- Pyrogenicity is a potential experimental variable that researchers should be aware of when using non-pharmaceutical grade agents.

4.10 Consideration should always be given to conducting a Pilot Study, and based on the information provided about the agent the IACUC may request one to be completed.

- If a novel agent is being tested, a pilot study using a minimum number of animals should be conducted to determine the dose and potential adverse effects. This would in turn help determine humane end point criteria specific to the project.

4.11 Common vehicle/diluents/solvents:

- Sterile water
- Physiological Salt Solution (e.g., 0.9% NaCl), PBS, balanced salt solution (e.g., Hanks)
- 60% (v/v) propane-1:2-diol (propylene glycol)
- 0.5% (w/v) carboxymethyl cellulose
- 10% (v/v) Tween 80 (polyoxyethylene (20) sorbitan mono-oleate)
- 10% (v/v) ethyl alcohol
- 50% (v/v) dimethylformamide
- 50% (v/v) dimethylsulfoxide (DMSO)
- Cyclodextrins5 (e.g. 2-hydroxypropyl-beta-cyclodextrin, Trappsol ®)
- Food/Diet

5.0 For more information on drug procurement, storage, disposal, controlled drugs and record keeping please see **Policy for Management of Pharmaceuticals.**

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Wolff, Axel (NIH/OD) [E]

From: Wolff, Axel (NIH/OD) [E]
Sent: Tuesday, July 24, 2018 11:10 AM
To: (b) (6)@unmc.edu)
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: FW: OLAW Case A3294-2F
Attachments: policy-for-management-of-pharmaceuticals.pdf; Policy for Nonpharmaceutical Grade Agents 7-18-18.pdf

Thank you for submitting these supporting documents, (b) (6) I will add them to the case file for completeness as well as Dr. Bradfield's explanation. I look forward to receiving the updated policy for handling pharmaceuticals upon completion. Please let Dr. Bradfield know that we appreciate receiving this information but will not send any additional response because the facts in the case have not changed and this information serves to supplement the overall case report.

Axel Wolff

From: (b) (6)@unmc.edu]
Sent: Monday, July 23, 2018 3:44 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: IACUCORA, UNMC <IACUCORA@unmc.edu>; Larsen, Jennifer L <jlarsen@unmc.edu>; Bennett, Robert G <rgbennet@unmc.edu>; (b) (6)@unmc.edu>; Bradfield, John F <john.bradfield@unmc.edu>
Subject: OLAW Case A3294-2F

Axel V. Wolff, M.S., D.V.M., Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
Rockledge 1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982

RE: IACUC Case #2018-01/OLAW Case A3294-2F

Dear Dr. Wolff,
As requested I have attached the UNMC/UNO IACUC policies for Management of Pharmaceuticals and Non-pharmaceutical Grade Agents that were recently updated and approved by the IACUC to address this reported incident.

Please let us know if you need anything else.

Respectfully,
(b) (6)

(b) (6)

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(b) (6)

From: Bradfield, John F
Sent: Wednesday, May 23, 2018 1:47 PM
To: Ward, Joan (NIH/OD) [E] <wardjoa@od.nih.gov>
Subject: RE: OLAW Case A3294-2F

Ms. Ward,

Thank you for sending the response from Dr Wolff regarding a report we sent to OLAW dated May 22, 2018 (Case A3294-2F). We would like to make a point of clarification of our report, involving the 10 nonhuman primates that had inadvertently received an incorrect drug. In its investigation of the incident, the IACUC determined that laboratory personnel had placed the order for the correct drug. On the drug order form completed by laboratory personnel and submitted to the company, the full name of the correct drug and its unique CAS number were provided. The drug company subsequently shipped the incorrect drug and identified it by the commonly used abbreviated name/ initials which unfortunately had the same abbreviated name/ initials as the intended drug. So the error was not that the incorrect drug was ordered, but rather because the incorrect drug was shipped and the drug label was inexact. Also, laboratory personnel did not validate that they had received the correct drug. Hence the error. This may seem a minor point, but it highlights the rather unique circumstances that contributed to the inadvertent drug substitution.

Dr Wolff's letter of today indicated that for completeness we should send, 1) the report by external experts who conducted a review of our drug handling practices and 2) any other policy changes. The report of the external review is a verbal report, so there is no documentation that we are able to provide. The IACUC policy for management of pharmaceuticals under revision and we will send that policy when the revision is complete.

Thanks again for your consideration and please let us know if you have any questions.

Best,

John

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W (b) (6)
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From: Ward, Joan (NIH/OD) [E] <wardjoa@od.nih.gov>
Sent: Wednesday, May 23, 2018 11:41 AM
To: Larsen, Jennifer L <jlarsen@unmc.edu>
Cc: (b) (6)@unmc.edu>; Bradfield, John F <john.bradfield@unmc.edu>; Schermerhorn, Jen (NIH/NIDA) [E] <jen.schermerhorn@nih.gov>
Subject: OLAW Case A3294-2F

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