Use of Non-Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals

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OLAW Online Seminar
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USDA Regulations Regarding the Use of Non-pharmaceutical Grade Compounds in Research

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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.**

(updated March 2011)

Pharmaceutical-grade Compound

Is any active or inactive drug, biologic, reagent, etc. which is approved by the FDA or for which a chemical purity standard has been written / established by any recognized pharmacopeia (book / compendia) such as:

- **US Pharmacopeia (USP),**
- **National Formulary (NF),**
- **British Pharmacopeia (BP),**
- **Pharmacopoeia of the Council of Europe (EP)**

Note the USP and NF have combined their standards into one compendia (USP-NF) http://www.usp.org/usp-nf

Guidance to IACUCs

Consider the following during protocol review:

- **The goals**
- **The justification**
- **The level of pain / distress**
  - Will purity differences result in toxic and adverse effects?
  - Will there be an increase in pain / distress?

    Consider Alternatives: National Agricultural Library- AWIC

    http://awic.nal.usda.gov or awic@ars.usda.gov
- **The procedure**
  - i.e. Survival Vs. Non-survival,

    Sterility would be a consideration

USDA Expectations

The wording of the regulations provides latitude for professional judgment, hence it is expected that the system of protocol evaluation serves as an opportunity for IACUC and investigators to work together in determining an optimal way to conduct experiments within the context of humane animal care.

Summary

- Policy 3: pharmaceutical grade compounds are to be used whenever available. Non-pharmaceutical-grade only used when the pharmaceutical grade is unavailable or when there is a scientific justification which has IACUC approval. Cost savings is not an acceptable justification.

- The USDA accepts the FDA definition of a pharmaceutical grade compound.

- The regulations provide latitude for IACUC and investigators to work together in determining an optimal way to conduct experiments within the context of humane animal care.

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AAALAC's Consideration of the Use of Non-Pharmaceutical-Grade Chemicals and Other Substances in Research with Animals

Christian Newcomer, VMD, DACLAM
Executive Director
OLAW Online Seminar, March 1, 2012

aaalacinternational

AAALAC's Position

- AAALAC is preparing a Frequently Asked Question on this issue
  - Anticipated release in spring 2012

- AAALAC expects institutions to comply with applicable regulatory requirements and guidelines

AAALAC's Assessment of NPG Drug Use: General Factors of Importance

Appropriate IACUC oversight and approval of use

1. Scientific justification provided and validated
2. Compliance with regional regulatory requirements / guidelines
3. Purity of compounds used should be U.S. Pharmacopeia grade or higher for therapeutic applications and whenever possible in research applications
4. Quality control / assurance factors:
   - Appropriate drug reconstitution, preparation &/or compounding
   - Drug purity, sterility, pH, osmolality, concentration, et cetera
   - Drug safety, efficacy, and shelf-life
   - Training, experience, and performance of personnel involved

AAALAC's Position

Referencing those requirements, AAALAC has experience historically in addressing this issue.

- AAALAC's approach to assessment of this topic is based upon performance standards.
- AAALAC has typically ranked its findings on this topic as Suggestions for Improvement and not Mandatory items.
- Clear, demonstrable adverse animal welfare outcomes related to NPG substance use could elevate the AAALAC ranking to a Mandatory item.

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OLAW's Position

- OLAW agrees with USDA that pharmaceutical-grade chemicals and other substances, when available, must be used to avoid toxicity or side effects.
- Frequently it is necessary to use investigational compounds, compounded drugs, and controlled substances (e.g., Schedule I controlled substances) in research activities to meet scientific and research goals.
- Use of non-pharmaceutical-grade substances must be justified and that justification must be reviewed and approved by the IACUC.

IACUC Responsibility

- May use a variety of administrative methods to review and approve.
  - E.g., may establish acceptable scientific criteria in lieu of case-by-case review.
- May consider relevant issues including safety, efficacy, availability, and introduction of new variables.
- Cost saving alone is not adequate justification.
- Principles also apply to non-survival studies.
- Agents for sedation, analgesia, anesthesia, or euthanasia must be pharmaceutical grade, unless justified and IACUC approved.

IACUC Evaluates Potential Adverse Consequences

IACUC may consider a number of factors including:

- Grade
- Purity
- Sterility
- Acid-base balance
- Pyrogenicity
- Osmolality
- Stability
- Site and route of administration
- Compatibility of components
- Side effects and adverse reactions
- Storage and pharmacokinetics

Not all factors may be applicable.

PI Responsibilities

In the animal study proposal, the investigator should identify any drugs, biologics, or reagents that will be administered to animals.

If these agents are not human or veterinary pharmaceutical-grade substances, provide a scientific justification for their use and describe the methods that will be used to ensure appropriate preparation and administration.

Specific Guidance to IACUCs

The next 4 slides contain examples of situations in which it would be reasonable for the IACUC to review and approve the use of non-pharmaceutical-grade substances.

IACUCs may use these examples as the basis for developing their own criteria.

These examples can be downloaded from the OLAW website at http://grants.nih.gov/grants/olaw/educational_resources.htm .

Example 1

1. When no equivalent veterinary or human drug is available for experimental use, then the highest-grade equivalent chemical reagent should be used and formulated aseptically, with a non-toxic vehicle, as appropriate for the route of administration.

Example 2

2. Although an equivalent veterinary or human drug is available for experimental use, the chemical-grade reagent is required to replicate methods from previous studies because results are directly compared to those of replicated studies.

Example 3

3. Although an equivalent veterinary or human drug is available, dilution or change in formulation is required.
   - If adulteration* by dilution, addition, or other change in formulation is required, there may be no additional advantage to be gained by using the USP formulation.
   - Use of the highest grade reagent may have the advantage of single-stage formulation and also result in purity that is equal to or higher than the human or veterinary drug.
   - Professional judgment should be used to determine the appropriate test material and to ensure use of an agent with the least likelihood for causing adverse effects.

   Veterinary and human drugs that are reconstituted according to the product insert remain pharmaceutical-grade drugs.

* Adulteration: addition of a substance that is used as an addition to another substance (does not imply impure, cheap, or unnecessary ingredient).

Examples 4 and 5

4. The available human or veterinary drug is not concentrated enough to meet experimental requirements.
5. The available human or veterinary drug does not meet the non-toxic vehicle requirements for the specified route of administration.

Questions?

We are not accepting questions during this webinar. Questions submitted to OLAW at olawdpe@od.nih.gov by March 30, 2012 will be answered by OLAW, USDA, and AAALAC. The questions and answers will be be posted on the OLAW website in the Education Resources Section associated with this webinar.

Questions

Are investigators required to use a compounding pharmacy when it is necessary to use a specific mixture of experimental drugs, chemicals or other formulations?

May investigators use a commercial compounding pharmacy to prepare specific mixtures of experimental drugs?

May investigators prepare the specific mixture themselves in the laboratory?

Question

What position or additional comments do USDA and AAALAC have on the issue of compounding?

Question

When it is necessary to add a vehicle or diluent to a chemical or substance that will be administered to an animal, is it required to use a pharmaceutical grade material?

Question

Does the requirement distinguish between the use of non-pharmaceutical-grade substances for medical / veterinary or research use?

Question

Does the requirement force us to use a more expensive substance that does not confer any additional benefits over a less expensive substance?

Question

Is the dilution of a drug such as Ketamine with saline for use in the mouse considered compounding?

Question

Can the IACUC approve the use of tribromoethanol (also known as Avertin)?

Avertin References

- Meyer, RE, et. al. "A review of tribromoethanol anesthesia for production of genetically engineered mice and rats." *Lab Anim (NY)*. 2005 34(10):47-52.
- Lieggi, CC, *et. al.* "An evaluation of preparation methods and storage conditions of tribromoethanol." *Contemp Top Lab Anim Sci*. 2005 44(1): 11-16.
- Zeller, W, *et. al.* "Adverse effects of tribromoethanol as used in the production of transgenic mice." *Lab Anim*. 1998 33(2):192-3.
- Lieggi CC, *et. al.* "Efficacy and safety of stored and newly prepared tribromoethanol in ICR mice." *Contemp Top Lab Anim Sci*. 2005 44(1):17-22.
- Tarin D, *et. al.* "Surgical anesthesia of mice: evaluation of tribromoethanol, ether, halothane and methoxyflurane and development of a reliable technique." *Lab Anim*. 1972 6(1), 79-84.

Question

Is it necessary to use USP or Grade A (Medical) CO_2 to euthanize rodents?

Questions

Can euthanasia solution be diluted and used as an anesthetic for survival surgery?

Can euthanasia solution be used as an anesthetic for non-survival surgery?

Question

Is it OK to use non-sterile euthanasia solution for euthanasia?

Question

Can non-pharmaceutical-grade pentobarbital be used for euthanasia?

Question

Does the NIH non-pharmaceutical-grade substance policy apply to aquatic species?

Question

OLAW FAQ F4 states, "…the IACUC may establish acceptable scientific criteria for use of these agents within the institution, rather than on a case-by-case basis." Can you give an example of how this might be used?
If the IACUC establishes an institutional policy in regards to use of a specific non-pharmaceutical-grade substance, what is required in an investigator's protocol?

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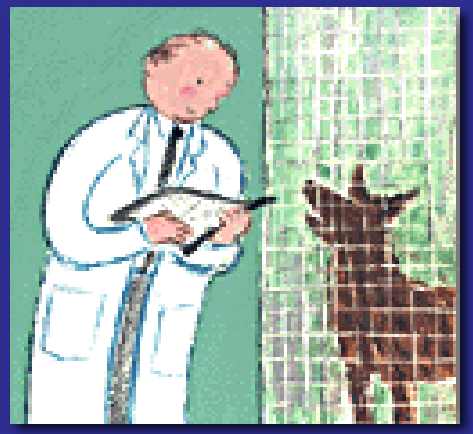
If you have additional questions or comments, submit them to OLAW at olawdpe@od.nih.gov by March 30, 2012. The questions will be answered by OLAW, USDA, and AAALAC. And posted on the OLAW website in the Education Resources Section associated with this webinar.

Presenters



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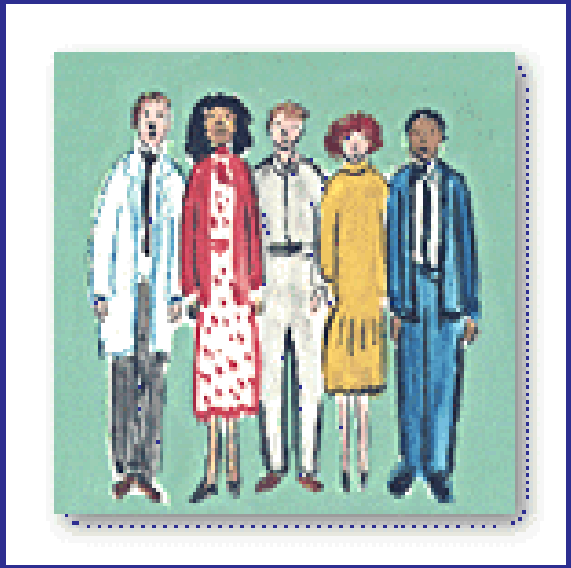

June 7, 2012

September 13, 2012

December 13, 2012