IACUC Policy on the Use of Non-Pharmaceutical Grade Compounds

Purpose

In December of 2011, NIH announced its decision to adopt the 8th Edition of the *Guide for the Care and Use of Laboratory Animals*. In response to the adoption, OLAW developed and posted Position Statements to clarify how Assured Institutions are to implement the *Guide*. OLAW Policy 3 states that pharmaceutical-grade compounds are to be used whenever available. Non-pharmaceutical-grade (NPG) compounds are 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.

Considerations

The IACUC is responsible for evaluating the potential adverse consequences of such agents when used for research. In making its evaluation for approval, the IACUC may consider factors including:

> Grade, purity, sterility, acid-base balance, pyrogenicity, osmolality, stability, site and route of administration, compatibility of components, side effects / adverse reactions, storage, pharmacokinetics

Although the potential animal welfare consequences of complications are less evident in non-survival studies, the scientific issues remain the same. The need for professional judgment outlined above apply to all studies including non-survival studies.

Procedures that may cause more than momentary or slight pain or distress to the animals must be performed with sedation, analgesia, or anesthesia agents using veterinary or human pharmaceutical-grade compounds, unless the use of an investigational chemical or formulation is scientifically necessary, appropriately justified, and approved by the IACUC. The use of a non-pharmaceutical-grade euthanasia agent must meet the same standards.

Justifications

Reasonable justifications provided for the use of non-pharmaceutical-grade substances include the following:

1. If no equivalent veterinary or human drug is available for experimental use, then the highest-grade equivalent chemical reagent should be used and formulated aseptically and with a non-toxic vehicle as appropriate for the route of administration.
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.
3. Although an equivalent veterinary or human drug is available, dilution or change in formulation is required.
    a. If adulteration by dilution, addition, or other change in formulation is required, resulting in no additional advantage gained by using the USP formulation.
    b. When 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.
    c. If it is determined that the NPG is an appropriate test material and the investigator can ensure use of the agent has the least likelihood for causing adverse effects.
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 injection.

Prohibitions

Avertin is the trade name for the injectable anesthetic 2, 2, 2 - tribromoethanol. Avertin was once manufactured as a pharmaceutical-grade drug, but is no longer available. For compliant use of tribromoethanol, the preparation and use of this anesthetic must be scientifically necessary, appropriately justified and approved by the IACUC. In making its decision the IACUC must consider the side effects, stability, storage requirements and other considerations associated with the preparation of this agent. There are multiple reports in the literature of physiologic harm to animals including ileus, adhesions and mortality from the use of tribromoethanol. OLAW advises IACUCs to critically evaluate the proposed use of tribromoethanol and consider alternative anesthetics that avoid or minimize discomfort, distress and pain. In addition an editorial published by *Cardiovascular Research* (2012) 93(1):1–3 includes the information that "6% of the total articles received in the past year for evaluation in *Cardiovascular Research* were rejected for ethical reasons. One of the most frequent causes of rejection on ethical grounds is the improper choice of anesthetic drugs for major surgical procedures." OLAW has been informed that the use of tribromoethanol was a factor.

A euthanasia solution **may not** be used as an anesthetic for survival or non-survival procedures. Euthanasia solutions cannot be diluted and used as an anesthetic for survival surgery. Typically these solutions are not sterile and contain drugs other than anesthetic agents that could harm or kill the animals even if diluted.