ASPET Comments to OLAW Regarding Adoption of the Guide for the Care and Use of Laboratory Animals: Eighth Edition

Re: Non-Pharmaceutical Grade Substances

The Association for Pharmacology and Experimental Therapeutics (ASPET) comprises 4800 members who are experts in research across a wide range of pharmacology specialties, as indicated by the names of its divisions: Behavioral Pharmacology, Cardiovascular Pharmacology, Drug Discovery & Development Drug Metabolism, Molecular Pharmacology, Neuropharmacology, Toxicology, and Translational & Clinical Pharmacology.

ASPET appreciates OLAW’s response to the 2010 public comment period in drafting a position statement to amplify its guidance on the research use of “Non-Pharmaceutical-Grade Substances.” The position statement is helpful in a number of respects: (1) in explicitly recognizing that the use of investigational compounds and Schedule I controlled substances frequently is necessary to meet research goals, (2) in advising that IACUCs may establish acceptable scientific criteria within their institutions for use of non-pharmaceutical grade agents, rather than requiring IACUC review and approval on a case-by-case basis; and (3) in providing a definition of a pharmaceutical grade compound.

Though the position statement was responsive to concerns about the paperwork and review burden that a strict interpretation of the 8th edition of the Guide on this topic imposes, it still reflects a view of pharmacology research that is at variance with the realities and practice of the science. We are concerned that unless these issues are clarified for IACUCs and scientists alike, research that uses drugs and other chemicals in laboratory animals will be unnecessarily, and likely inadvertently, impeded. The far-reaching importance of this issue is clear given that pharmacology research in laboratory animals is a part of the portfolio of virtually every NIH Institute.

Below are specific comments on Position Statement 3.

Differentiation of clinical and research use of drugs:

The statement that OLAW and USDA agree that pharmaceutical grade chemicals must be used to avoid toxicity or side effects, as written, implies that the USDA has precluded use of "non-pharmaceutical grade" chemicals in research procedures. To our knowledge, this is not the case. Rather, policies in the USDA/APHIS Policy Manual are restricted to interpretation of the Animal Welfare Act (AWA) Regulations with respect to covered species. Their Policy 3 interprets 9 CFR, Part 2, Section 2.31 "(d). (1). . . . Further, the IACUC shall determine that the proposed activities or significant changes in ongoing activities meet the following requirements:. . . . (i.v.) Procedures that may cause more than momentary or slight pain or distress to the animal will: (A) Be performed with appropriate sedatives, analgesics or anesthetics, unless withholding such agents is justified for scientific reasons, in writing, by the principal investigator and will continue for only the necessary period of time . . . . "

American Society for Pharmacology and Experimental Therapeutics
Thus we conclude that USDA Policy 3 covers only “sedatives, analgesics, or anesthetics” used to prevent pain/distress with species covered under the AWA. It does not pertain to those situations in which a drug is being used as a research tool or to study its effects, which is implied by the current wording in the OLAW position statement and in the 8th edition of the Guide itself. We urge that OLAW clarify a distinction in policy between drugs for clinical use in research animals and those selected for use to accomplish the scientific aims of the research.

Implications that drugs not formulated for clinical use are inferior for research use:

The first sentence of Position Statement 3 that “. . . pharmaceutical grade chemicals and other substances, when available, must be used to avoid toxicity or side effects that may threaten the health and welfare of vertebrate animals and/or interfere with the interpretation of research results,” followed by “However, it is frequently necessary to use investigational compounds, veterinarian- or pharmacy-compounded drugs, and/or Schedule I controlled substances to meet scientific and research needs” attributes liabilities and risks to research compounds that do not apply. In fact, researchers are particularly sensitive to assuring that variables that would jeopardize the research and its interpretation are identified and controlled.

Furthermore, were researchers to attempt to use a preparation sold for clinical use for dose-effect evaluations, which are central to pharmacology research, they inevitably must manipulate that solution in ways that might indeed introduce the toxicity and uncontrolled variables that are the topics of OLAW’s concern to the research. Specific problems with clinical use solutions for pharmacology research were covered in our submission during the comment period. We urge that the position statement wording be changed to remove the implication that drugs selected for research purposes will necessarily be inferior to those that have been formulated for clinical use.

We appreciate the inclusion of reference to Schedule I controlled substances as those that may be used in research, and also that footnote 3 also states that Schedule II-V drugs may be used in biomedical research. It would be helpful to include the reference to Schedules II-V in the body of the position statement. In addition, it would be reasonable to acknowledge the NIH/NIDA drug supply programs for funded researchers as a recognized source of drugs for animal research.

The definition of a pharmaceutical grade drug footnote 1 is an important step forward, and we appreciate that this has been adapted from guidance prepared by the NIH intramural research program. Given the concerns implied in the position statement regarding drug quality, we believe that the position statement should bring the issue of drug purity prominently into the discussion of the types of compounds that may be used appropriately in research. In fact, there are companies that, for decades, have been highly regarded vendors of compounds of excellent quality for laboratory animal research. These companies typically supply technical information on purity and other qualities of the compounds with each purchase. In many cases, these products are of equal or higher purity as those manufactured as USP grade. Exclusion of mention of such sources and their dependability could be taken by IACUCs to mean that their products are inferior for research needs, when, in fact, they are often the best quality for a research purpose.

Expertise necessary to formulate drugs for research use:

The position statement includes the possibility that research “drugs,” (presumably solutions) may be compounded by a veterinarian. This suggests that researchers should be encouraged to turn their investigational drugs over to a veterinarian for preparation for research use. We suspect this is not what was intended. The link supplied to the AVMA website (in footnote 2 of the position statement) indicates that this AVMA policy was generated to permit veterinarians in clinical practice to prepare a drug from powder in case the one that was needed for clinical use were to be unavailable commercially, which is consistent with the policy expressed in USDA/APHIS Policy 3 regarding medications that are unavailable.
We suggest that it would be inappropriate (and likely unwelcome) to ask institutional veterinarians to prepare research compounds for investigators.

The position statement also seems to urge researchers to turn powder forms of drugs over to a pharmacy for preparation of solutions, which is problematic. In addition to the practical and cost-related issues, the individuals most qualified to determine how to prepare and store compounds for a particular research use are most often the investigators themselves. Many research compounds must be used within a short period of time after being solubilized and/or stored under special conditions, and it is unrealistic to imply to IACUCs that locating a compounding pharmacy is a first choice for preparation of solutions for research. Investigators who carry out drug research typically are well versed in the considerations relevant to the compounds they are using; and have equipped their laboratories with the analytical balances, stirrers, pH meters, sonicators, etc. necessary for drug preparation. In fact, even with respect to medications for sedation, analgesia, and anesthesia that are unavailable in clinical use formulations, an investigator’s laboratory may be better experienced and equipped to prepare these appropriately than are veterinary facilities at many research institutions.

With respect to compounds legally scheduled under the Controlled Substances Act, researchers who obtain these drugs by virtue of their approved DEA and state registrations have committed to procedures for secure storage, record-keeping and supervision of use by limited numbers of individuals. Turning such compounds over to another entity for formulation of solutions raises unnecessary legal complications in addition to those described above.

We agree with the position statement comment in the paragraph on non-survival studies that “professional judgment” of the investigator is the key element to determine that scientific issues are appropriately addressed in choice of formulation for a research study. We urge that the wording that implies that only veterinarians and pharmacists are qualified to prepare drugs for administration be revised to focus on the importance of the expertise of the investigator with respect to selection, handling, and use of compounds in research as the primary consideration.

Cost considerations and animal welfare:

We agree with OLAW that it is critical to take animal welfare into consideration in making choices of procedures and materials to use in laboratory animal research. Certainly one should not make poor choices of drugs based on cost. However, we are concerned that the position statement, as well as the previous FAQ and the Guide itself, impose requirements to choose a more expensive option when a less expensive option will indeed be entirely appropriate for the research and for the welfare of the animal. Given that funds for purchase of chemicals and drugs for research within NIH and at Assured institutions come from federal research budgets, we urge OLAW to recognize that, other considerations being equal, cost savings are an important consideration in making choices for research materials.

Conclusion:

We acknowledge that the 8th edition of the Guide did indeed incorporate a position that OLAW had taken with its publication of an FAQ in Lab Animal in 2003, and regret that we and others did not formally address this issue several years ago. However, our focus on it in the context of the adoption of the 8th edition of the Guide is, to some extent, now usefully informed by experience with IACUC approaches to compliance with the FAQ statements themselves.

We appreciate this opportunity to comment on behalf of our membership. We hope that OLAW will feel welcome to contact ASPET for discussion of any of the concerns related to use of drugs and other chemicals in laboratory animals as it reviews our and other comments on this position statement.