Clarification on a contradiction

To the Editor — In reviewing OLAW's response to the Protocol Review scenario presented in the June 2018 issue of Lab Animal[1], I noted a direct contradiction to previous advice regarding Veterinary Verification and Consultation (VVC) review of changes from pharmaceutical to non-pharmaceutical compounds issued by OLAW in their August 21, 2014 webinar entitled, "Significant Changes to Animal Activities."

Specifically, in Dr. Brown's response to the scenario presented in the column she states, "Neither the change to a non-pharmaceutical grade version nor to an outdated drug qualify as acceptable practices for an IACUC to include in its VVC policy". Yet in the OLAW webinar transcript[2], it states:

Q10: Can the IACUC have a policy allowing the change from a pharmaceutical grade substance to a non-pharmaceutical-grade substance?

A10: Yes, the IACUC may develop an institutional policy regarding the use of non-pharmaceutical-grade substances. OLAW FAQ F4 states, *OLAW and USDA agree that pharmaceutical-grade chemicals and other substances, when available, must be used… 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 goals… The IACUC may use a variety of administrative methods to review and approve the use of such non-pharmaceutical grade agents. For example, the IACUC may establish acceptable scientific criteria for use of these agents within the institution, rather than on a case-by-case basis*. Change from a pharmaceutical-grade to non-pharmaceutical-grade substance according to an IACUC-approved policy may be administratively handled by veterinary verification and consultation as per NOT-OD-14-126, paragraph 2a., change in experimental substances.

Given that researchers frequently have legitimate reasons to switch from pharmaceutical to non-pharmaceutical grade compounds and given the strong interest in the use of VVC, I feel that clarification regarding these contradictory statements should be provided. ❐

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1. Brown, P. *Lab Anim (NY)* **47**, 141 (2018).
2. Office of Laboratory Animal Welfare, National Institutes of Health. Significant Changes to Animal Activities. Webinar. https://olaw.nih.gov/sites/default/files/140821_seminar_transcript.pdf (2014).

Reply to "Clarification on a contradiction"

In response to a request to clarify the appropriate use of veterinary verification and consultation (VVC) in the Protocol Review column, *What's the appropriate adjustment when an approved drug is in short supply?*[1], OLAW offers the following clarification:

In the Lab Animal column, OLAW responded to a scenario in which a PI requested permission to use a recently outdated analgesic or a reference standard version of a drug as the negative control in an ongoing study stating:

> *Neither the change to a non-pharmaceutical-grade version nor to an outdated drug qualify as acceptable practices for an IACUC to include in its VVC policy. Additionally, a change to administer the reference standard, which is not formulated for clinical use, has the potential to result in greater pain or distress to the animal, which is prohibited from the use of VVC. For these reasons, the veterinarian must refer this request to the IACUC. Using VVC to select from a list of approved drugs is acceptable.*[1]

However, in the OLAW special webinar *Significant Changes to Animal Activities*, broadcast August 21, 2014, Question 10, OLAW stated:

> *Change from a pharmaceutical-grade to a non-pharmaceutical-grade substance according to an IACUC approved policy may be administratively handled by veterinary verification and consultation as per NOT-OD-14-126, Guidance on Significant Changes to Animal Activities paragraph 2a., change in experimental substances.*[2,3]

OLAW instituted the VVC mechanism in support of the use of performance standards and professional judgment and to reduce regulatory burden. The VVC policy was developed to enable institutions to have increased flexibility to meet the demands of biomedical research and humane animal care and use while remaining in compliance with the standards of the PHS Policy. As such, the VVC method of approval of significant changes to previously approved animal activities, is a two-part approval process. The first part of the process occurs when the IACUC develops and approves a VVC policy that incorporates specific reference documents (e.g., guidance documents, institutional policies, standard operating procedures, drug formularies) to address significant changes frequently requested at the institution. The second part of the approval process occurs when the IACUC-designated veterinarian verifies through consultation with the research team that the requested significant change 1) meets the intention of the IACUC in its previously approved policy, 2) is appropriate for the specific needs of the animal(s) in question, and 3) is compliant with all requirements of NOT-OD-14-126 to include documentation of the protocol change.

NOT-OD-14-126 excludes the changes described in 1.a-g. These specific changes must be approved by either FCR or DMR. Applicable to this scenario, NOT-OD-14-126 1.b. requires that any change resulting in greater pain or distress to the animal(s) be approved by FCR or DMR.

A significant change from a drug formulated for use in an animal to the administration of a reference standard is not acceptable for the use of VVC. A reference standard, developed for the calibration of instruments, has the potential to inflict increased pain and distress on the animals, as it has not been developed in consideration of efficacy, purity, pH, sterility, and other critical physiologic consideration. Similarly,

an outdated drug is designated expired because the manufacturer does not certify that it meets efficacy standards. Therefore, the outdated drug may reasonably be suspected of having the potential to increase pain and distress to the animal.

The Lab Animal scenario did not specify the existence of policies developed by the IACUC relevant to the requested significant change. If the IACUC had an approved policy designating the specific conditions under which a change from a previously identified pharmaceutical-grade drug to a non-pharmaceutical-grade version were acceptable, this change could have been considered under that policy. Such a policy would have been developed to be in congruence with OLAW FAQ F4[4]. Specifically, the IACUC is responsible for evaluating the potential adverse consequences of non-pharmaceutical-grade substances when used for research. In making its evaluation, the IACUC may consider factors including, for example: 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. It is more likely that the IACUC would develop such a policy to enable investigators to develop modified experimental substances under testing. The VVC two-part method of modifying previously approved significant changes reduces burden when it addresses significant changes that are commonly encountered. The current scenario appears to be an unlikely VVC candidate because it is a singular need that does not lend itself to the development of a standard policy applicable to future needs. Therefore, development and approval of the policy would increase burden on the IACUC without reducing burden on the investigator. ❐

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4. Office of Laboratory Animal Welfare, National Institutes of Health. Frequently asked questions: PHS Policy on humane care and use of laboratory animals. https://olaw.nih.gov/guidance/faqs#useandmgmt_4 (2017).