A WORD FROM OLAW

In response to the issues posed in this scenario, the Office of Laboratory Animal Welfare (OLAW) provides the following clarifications:

In this scenario, a PI requests permission to use a recently outdated analgesic or a reference standard version of the drug as a negative control in an ongoing study. The request for the change came via the Veterinary Verification and Consultation (VVC) method to the veterinarian who referred it for full committee review (FCR). The scenario asks, “Should the IACUC approve the use of the outdated drug, the reference standard, or take an entirely different approach?” and “Was the VVC method being used appropriately?”

In this study, buprenorphine is used as an experimental substance, not as a clinical analgesia agent. The continued use of pharmaceutical-grade buprenorphine is the best approach to avoid putting the research on hold or compromising the validity of the controls. In response to the drug shortage, choices to consider include 1) canvassing a wider group of institutions to obtain non-expired product, or 2) contacting the manufacturer regarding the potency and efficacy of “recently outdated” buprenorphine. Using the expired drug without such verification may add an uncontrolled variable to the study. Using the reference standard for a different purpose than listed on the product insert is unacceptable unless it can be demonstrated to the satisfaction of the IACUC that 1) there is no variation between the reference standard and the pharmaceutical product in safety or efficacy, and that 2) the purity,

sterility, acid-base balance, pyrogenicity, and other attributes of the substance when administered will not negatively impact animal welfare or compromise the study^{1,2}.

The veterinarian may refer any VVC request to the IACUC for review for any reason and must refer any request that does not meet the parameters of the IACUC-reviewed and -approved policies.³ Neither the change to a non-pharmaceutical-grade version nor to an outdated drug qualify as acceptable practices for an IACUC to include in its VVC policy.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.³ Using VVC to select from a list of approved drugs is acceptable. □

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2. National Institutes of Health, Office of Laboratory Animal Welfare. *Frequently Asked Question F.5: PHS Policy on Humane Care and Use of Laboratory Animals*. <https://grants.nih.gov/grants/OLAW/faqs.htm#663> (2017).
3. National Institutes of Health. *Guidance on Significant Changes to Animal Activities*. Notice NOT OD-14-126 (National Institutes of Health, Washington, DC, 26 August 2014) <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html>

circumstances. Therefore, even though the expired buprenorphine would be used as a negative control for an experimental procedure, its use would be contradictory to OLAW recommendations and should not be approved¹.

The use of pharmaceutical-grade compounds is preferred to ensure that toxic or unwanted side effects are excluded from studies conducted with experimental animals, and these compounds should be used, when available, for all animal-related procedures. However, non-pharmaceutical-grade substances may be used to meet scientific goals or when veterinary or human pharmaceutical-grade products are unavailable if their use is described

and appropriately justified in an approved animal use protocol². In this scenario, because the buprenorphine is being used as a negative control in an ongoing study and a different analgesic cannot be substituted, non-pharmaceutical-grade buprenorphine would be suitable for meeting the scientific goals of the research. In addition, since the pharmaceutical-grade product is unavailable, it would be appropriate for the IACUC to consider approving an amendment justifying the use of the non-pharmaceutical-grade formulation under these circumstances. However, before approving its use, the IACUC should consider the purity, sterility, pH, pyrogenicity, osmolality, stability, site

and route of administration, formulation, compatibility, and pharmacokinetics of the non-pharmaceutical-grade buprenorphine². The IACUC should also consider whether the use of non-pharmaceutical-grade buprenorphine is compliant with guidelines and requirements of applicable national or regional regulatory and relevant funding agencies; and whether its preparation, labeling (i.e., preparation and use-by dates), administration and storage meets the aim of maintaining stability and quality (i.e., to prevent inadvertent co-administration of infectious agents or contaminants)³.

The Veterinary Verification and Consultation (VVC) process provides IACUCs with the flexibility to allow specific significant changes, such as changes in analgesics or experimental substances, to be handled administratively in consultation with a veterinarian authorized by the IACUC and in accordance with IACUC-approved policies⁴. With respect to non-pharmaceutical grade compounds, an IACUC may establish acceptable scientific criteria for their use within its institution, rather than approving their use on a case-by-case basis. These criteria should reflect relevant animal welfare and scientific issues such as safety, efficacy, unavailability of pharmaceutical-grade compounds, and inadvertent introduction of new variables⁵. If Dr. Rosenfeld's IACUC had established criteria in the form of an IACUC approved institutional policy, the VVC process could have been appropriately used to approve her request. In this situation, without such a policy, the veterinarian followed the VVC procedure correctly by redirecting the request to the IACUC. □

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4. National Institutes of Health. *Guidance on Significant Changes to Animal Activities*. Notice NOT-OD-14-126. (National Institutes of Health, Washington, DC, 26 August 2014).
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