What's the appropriate adjustment when an approved drug is in short supply?

The Rosenfeld laboratory was researching the efficacy in rodents of certain new synthetic opioids when a nationwide shortage of buprenorphine hydrochloride occurred. Buprenorphine was being used as a negative experimental control because previous research demonstrated that the drug was not effective in alleviating the induced neuropathic pain that was being studied. "Not a problem," said Lonny Lyons, one of the post-docs in the lab, "we have USP buprenorphine reference standard from some earlier work and we'll just use it instead of the commercial drug." But when the request for the change reached the attending veterinarian for concurrence via the Veterinary Verification and Consultation (VVC) method, the veterinarian said she was not able to concur with the request because the literature provided by the vendor of the reference standard said that it was not intended to be used as a drug.

Still undaunted, the lab requested that it be allowed to use its recently outdated commercial buprenorphine hydrochloride, and they provided the IACUC with literature citations that claimed most drugs can be used well past their expiration dates without a loss of efficacy. Accompanying the request was a note from Dr. Rosenfeld explaining that she could not substitute a different negative control drug in the middle of her research. The veterinarian referred the request to the full committee which was meeting in a few days. At that meeting she said that upon reflection, she did not think that either the outdated buprenorphine or the buprenorphine reference standard would create an animal welfare issue, but she was reluctant to verify the use of either of those products without IACUC input. She added that she had tried borrowing in-date buprenorphine from nearby colleagues, but her attempts were unsuccessful.

Do you think that the IACUC should agree with the use of the outdated drug, the reference standard, or take an entirely different approach? Was the VVC method being used appropriately? ❐

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Achieving the desired outcome

The scenario states that buprenorphine is administered to rodents as a negative control in a study evaluating the efficacy of certain new synthetic opioids; however, a nationwide shortage of buprenorphine has occurred. The IACUC is faced with the challenge of trying to decide if it is acceptable for Dr. Rosenfeld to use outdated buprenorphine or a buprenorphine reference standard to complete her study. The IACUC's policy on veterinary verification and consultation (VVC) is not provided in this scenario, but it seems unlikely that the policy would address the use of either a reference standard or an expired drug, so the Attending Veterinarian was correct in referring the request to the full committee.

An understanding of what a drug reference standard is would be helpful to the IACUC in evaluating this problem. "A reference standard is a substance prepared for use as the standard in an assay, identification, or purity test and should have a quality appropriate for its use[1]." As noted in the scenario, reference standards are not intended to be used as a drug. The United States Pharmacopeia (USP) states, "USP Reference Standards are not for use in humans or animals as drugs or medical devices. They are intended for test and assay use only as per their associated USP compendial application(s)[2]." Given this information, the use of the buprenorphine reference standard in Dr. Rosenfeld's study would not be an acceptable solution. Furthermore, the drug reference standard may yield results that differ from those obtained using the commercial buprenorphine product.

Today's standard of veterinary care does not recognize the use of expired drugs, biologics, and medical supplies as an acceptable practice[3]. However, performance standards may be used to address a variety of issues related to humane animal care and use. The *Guide* states, "Performance standard means a standard or guideline that, while describing a desired outcome, provides flexibility in achieving this outcome by granting discretion to those responsible for managing the animal care and use program, the researcher, and the IACUC. The performance approach requires professional input, sound judgment, and a team approach to achieve specific goals... Performance standards can be advantageous because they accommodate the consideration of many variables... so that implementation can be best tailored to meet the recommendations in the Guide[4]." OLAW's position on performance standards says that"a well-developed performance standard meets the following criteria: supports scientific objectives, supports the health and welfare of the animal; includes a justified performance index; and has associated outcome criteria[5]." In this case, the IACUC and Dr. Rosenfeld could develop a performance standard for the use of an expired drug stating that it is essential to the experiment; it is not (currently) commercially available; it has been verified to be safe and effective for use in animals through laboratory verification of potency, sterility, stability, and other parameters; and the results obtained using the expired drug are expected to be consistent with previously collected data that used the commercial buprenorphine product. The IACUC may also want to request documentation be obtained from the manufacturer of the expired buprenorphine that the product can be used past its expiration date for a specified length of time without a loss of efficacy.

If all the performance standard criteria are met, the IACUC could vote to approve an amendment on the use of expired buprenorphine in Dr. Rosenfeld's study until in-date buprenorphine is available for purchase. A performance standard is not a departure from *Guide*, and its use is

encouraged by OLAW if applicable[5]. If the IACUC finds the use of recently expired buprenorphine does not meet the required outcome or rejects the performance standard concept outright, the only other option would be for the entire project to be placed on hold until the appropriate, in-date buprenorphine drug product is available. ❐

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Considering animal welfare with scientific justification in mind

The scenario has two components to be considered: animal welfare and scientific justification.

In consideration of animal welfare, the IACUC should not agree with the use of the outdated drug or the reference standard. The US Pharmacopeia clearly states that the reference standards are meant to be used in tests and assays, and not in humans and animals[1]. Therefore, the safety and the pain control properties of the reference standard are not guaranteed in rodents; using it in this study could risk unexpected adverse effects or insufficient pain control. Outdated buprenorphine HCl should also not be used; while there may be literature that vouches for acceptable efficacy in outdated buprenorphine HCl, the reality could depend on many variables, such as the manufacturer, the length of expiration, and the specific species, sex, and strains of the animals. Furthermore, approving the usage of USP or outdated drugs comes with two risks: first, this may set a precedent for future similar requests; second, if the rodents that received USP or outdated buprenorphine HCl suffered an adverse event, the IACUC and the veterinarian could be held responsible. According to the *Guide for the Care and Use of Laboratory Animals*, expired anesthetic and analgesic agents should not be used[2] . Taken together, the IACUC should not approve this request.

Another reason why the request from the Rosenfeld lab should not be approved is inadequate scientific justification. Using either of these choices would create a variable that could render the results incomparable with previous work. If Dr. Rosenfeld does not wish to use a different negative control in the middle of the study, then neither USP nor outdated buprenorphine HCl should be used. Creating variables like this could result in unusable data and unnecessary use of animals. The IACUC could instead suggest the lab use buprenorphine SR (assuming that only the HCl formulation is in shortage), if this formulation is acceptable for the lab.

The use of VVC is initially correct in this case because the consultation was for using a different drug in response to a shortage of the original one, which falls within the parameter of a VVC[3]. However, because the lab's request to use USP or outdated buprenorphine HCl is not based on the need for pain management, this issue becomes one where the PI needs to scientifically justify the use of alternative drugs at the risk of animal welfare. Therefore, the veterinarian is correct in bringing this issue to the IACUC.

In the event of drug shortage of unknown duration, it is understandable that investigators would want to carry on the project instead of waiting indefinitely. The IACUC must not forget that animal lives could be wasted too if the project is delayed. Prior to making a definitive decision, the IACUC must carefully consider the justification provided by the investigators. ❐

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Redirecting the request to the IACUC

Due to the shortage of pharmaceutical-grade buprenorphine, the IACUC and Attending Veterinarian are faced with the challenge of determining which situation is more appropriate: allow Dr. Rosenfeld to use non-pharmaceutical-grade buprenorphine, allow her to use expired pharmaceutical-grade buprenorphine, or allow neither, postponing the research until pharmaceutical-grade buprenorphine becomes available.

Guidance provided by OLAW indicates that use of expired analgesics is inconsistent with acceptable veterinary practices and adequate veterinary care. OLAW does not provide for the use of analgesics beyond their expiration date under any

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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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 approved[1].

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 protocol[2]. 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 buprenorphine[2]. 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 policies[4]. 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 variables[5]. 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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