# Frequently Asked Questions About the Public Health Service *Policy on Humane Care and Use of Laboratory Animals*

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**The authors answer eight questions commonly asked of the Office of Laboratory Animal Welfare concerning the Public Health Service *Policy on Humane Care and Use of Laboratory Animals.***

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The Office of Laboratory Animal Welfare (OLAW) of the National Institutes of Health (NIH) develops, implements, and oversees compliance with the US Public Health Service (PHS) *Policy on Humane Care and Use of Laboratory Animals*[1] (*Policy*). The PHS *Policy* and the US Department of Agriculture's (USDA's) Animal Welfare Regulations[2] are the two principal federal documents that set forth requirements for animal care and use by institutions using animals in research, testing, and education. One of OLAW's primary functions is to assist institutions in implementing PHS *Policy* by responding to policy-related questions. This is accomplished by collaborating with organizations and individuals in preparing guidance for Institutional Animal Care and Use Committees (IACUCs)[3–5], supporting the publication of monographs on various aspects of animal care and use programs[6,7], and publishing *Policy* interpretations in articles[8–18] and other formats[19–30]. OLAW also sponsors seminars and training that specifically address current topics covering animal care and use, and issues guidance notices in the NIH Guide for Grants and Contracts (formerly as "Dear Colleague" letters), all of which are found on the OLAW website (http://grants.nih.gov/grants/olaw/olaw.htm). The following represent several additional questions frequently asked by institutions and the OLAW responses.

**1. Does the IACUC need to require that the investigator submit the grant application, or portions thereof, along with the IACUC animal use protocol form for review by the IACUC? Is the IACUC required to compare the two for consistency?**

PHS *Policy* (IV.D.) requires the institution to verify, before award, that the IACUC has reviewed and approved those components of grant applications and contract proposals related to the care and use of animals. This position is reiterated in NIH Grants Policy Statement under Part II, Terms and Conditions. Most institutions have developed an IACUC protocol form and require investigators to provide detailed information about the proposed use of the animals on this form. The signature of the authorized institutional official on any PHS application or proposal indicates the organization's commitment to comply with the laws, regulations, and policies to which an activity is subject. Institutional submission of IACUC approval, subsequent to submission of the application/proposal, must represent approval of the information originally submitted in the application/proposal, or include notification of any significant changes required by the IACUC.

Although there is no explicit requirement for the IACUC to do a side-by-side comparison of the application/proposal and the IACUC protocol review form, it is an institutional responsibility to ensure that the information the IACUC reviews and approves is consistent with that contained in the application/proposal to be funded. Institutions are free to devise a workable mechanism to accomplish this end. One excellent way to prevent problems of inconsistencies between the information submitted to the PHS and that on the IACUC protocol review form is to implement a procedure for direct compar-

ison[23]. If a procedure of direct comparison is adopted, the individual(s) charged with conducting the comparison should be appropriately qualified to identify inconsistencies. Some institutions have delegated this responsibility to a particular office or position (*e.g.*, sponsored programs office, compliance office); others have asked Departmental Chairs to verify consistency[31].

**2. Our IACUC has several categories for the approval of animal study protocols. Which one to use depends on the kinds of issues it identifies during review. We are sometimes unsure how best to characterize the approval status of these projects. Can OLAW provide any advice as to what constitutes appropriate terminology for approval of a protocol?**

The PHS *Policy* recognizes only three outcomes of IACUC reviews of proposed activities (protocols) related to animal care and use, as well as proposals for significant changes in previously approved ongoing activities. They are 'approve', 'withhold approval', and 'require modifications to secure approval'. OLAW is aware that some institutions have chosen to use different words and phrases to characterize the latter of these outcomes, such as 'conditionally approved', 'approval pending', 'provisionally approved', 'approved with stipulations', 'administrative approval', and 'limited approval'. We should note that several incidents of suspensions and noncompliance are reported by institutions to OLAW each year that are related to the conduct of unauthorized animal studies by investigators who have misinterpreted IACUC responses or the approval categorization of their proposals. To avoid such misunderstandings and the subsequent necessities to take corrective actions and report to OLAW, this Office recommends that IACUCs use language that is as unambiguous as possible in communicating the results of their reviews of animal study protocols. We suggest that institutions can do this by adhering to the language of the *Policy* and avoiding use of the words 'approved' and 'approval' to describe the outcome of any review that is not an unequivocal approval and making it known that no animal work may commence without an unequivocal approval. In addition, the IACUC approval date submitted to PHS agencies as part of a grant application or contract proposal must reflect the date of final approval.

**3. Are the scientists at our institution allowed to use non-pharmaceutical-grade chemical compounds in physiological preparations involving laboratory animals? Please clarify whether this is an allowable practice and whether it makes a difference if the compounds are used in survival versus nonsurvival experiments.**

The use of non-pharmaceutical-grade chemical compounds in experimental animals under certain circumstances has been, and will continue to be, a necessary and acceptable component of biomedical research. OLAW and the USDA have determined that their use should be based on (1) scientific necessity, (2) nonavailability of an acceptable veterinary or human pharmaceutical-grade compound, and (3) specific review and approval by the IACUC[32]. In preparing and reviewing proposals to use non-pharmaceutical-grade products, investigators and IACUCs should consider a number of related animal welfare and scientific issues including safety, efficacy, and the inadvertent introduction of research-complicating variables. Although one can assume that issues such as sterility, pyrogenicity, stability, pharmacokinetics, and quality control have been addressed during the course of producing pharmaceutical-grade drugs, one cannot say the same for substances produced in the research laboratory using non-pharmaceutical-grade chemical compounds. Cost savings alone do not adequately justify the use of non-pharmaceutical-grade compounds in animals. Although the potential animal welfare consequences of complications are less evident in nonsurvival studies, the scientific issues remain the same. The principles and need for professional judgment just outlined still apply.

**4. Because of time constraints and the needs of our investigators, our IACUC reviews some protocols by sending each member a copy and then polling them to determine whether they approve. Is this procedure in compliance with the PHS *Policy* if the IACUC members, at a subsequent full-Committee meeting, are asked to reaffirm their votes? Is this procedure appropriate, and if not, what must we do to correct the situation?**

No. The initial polling of members is not sufficient for approval and initiation of work on animals. Only full Committees or designated members can approve animal study protocols, in accordance with the PHS *Policy* (IV.C.2). IACUC members may use electronic or other forms of polling to call for a full-Committee review, but not to vote[12,17]. Any animal studies undertaken on the basis of approvals resulting from such polling would not be compliant with the PHS *Policy*. Recognizing that urgency may sometimes be an issue in considering animal study protocols, the PHS *Policy* allows for designated review by at least one qualified member, appointed by the IACUC Chair, provided that all other voting members have had an opportunity to request full review and that no member requests a full-Committee review.

**5. Several investigators at our institution wish to use surgically modified anmals in their research but do not want to perform the surgery in-house. We are considering the purchase of such animals and would like to know whether the PHS *Policy* applies to customized surgery peformed at vendor facilities.**

The PHS *Policy* is applicable to all PHS-supported activities involving animals, whether the activities are performed at a PHS agency, an awardee institution, or other institution (PHS *Policy* at I., II., III., and V.B.). OLAW has provided guidance regarding animal use (antibody production) that takes place outside the applicant/assured institution through subgranting or subcontracting[33]. That guidance may also serve as a template for determining whether other activities such as

customized surgery are covered by the PHS *Policy*. In this regard, and with respect to applicability of the PHS *Policy*, a determining issue is whether the surgery is conducted in response to a specific custom request or whether the animals were previously modified and available before the request was made. If an investigator requests that a specific custom surgical procedure or procedures be performed on an animal for use in activities funded by the PHS, then the organization that conducts the procedure(s) is considered a performance site and must either have on file with OLAW an approved Animal Welfare Assurance or be included as a component of the applicant organization's Assurance.

**6. We are a small antibody producer using rabbits, mice, and goats, and our work supports numerous clients, including some funded by the PHS. When we applied for an Assurance, OLAW informed us that we could not approve one 'blanket protocol' to cover all of our antibody production procedures, even though the work is essentially always the same. Please clarify.**

Provisions of the PHS *Policy* apply to all Assured institutions regardless of their size or mission. They include the requirement for the IACUC to "review and approve, require modifications in (to secure approval) or withhold approval of those components of PHS-conducted or supported activities related to the care and use of animals," (PHS *Policy* at IV.B.6.) on a project-specific basis. Consequently, each proposed protocol involving antibody production as well as significant changes (e.g., amendments) to previously approved protocols must be submitted for IACUC review and approval, taking into account the aims of the study and the methods proposed to avoid or minimize pain or distress to the animals (PHS *Policy* at IV.C.1.). For example, reviews of proposed ascites monoclonal antibody production in mice must also critically address alternative (*in vitro*) methods as well as pain and distress issues[6,33]. Another example would be a request for a custom antibody against a specific protein for the purpose of vaccine development, followed by a request for an antibody against a different protein to be used for the same purpose. In both instances, *Policy* would require either an amendment or a new protocol. As is the case with any new protocol or proposed significant change to a previously approved protocol, the PHS *Policy* allows for either full-Committee or designated-member review. OLAW recognizes that many aspects of antibody production are routine and recommends that institutional Standard Operating Procedures (SOPs) be developed that describe species-specific techniques for immunization, titer determinations, volume blood collection, and associated procedures. One may cite IACUC-approved SOPs in proposed project-specific protocols or proposed amendments to avoid needless repetition. Under these circumstances, it is possible to combine multiple projects, or even multiple investigators, under a single protocol. However, for PHS *Policy* purposes, IACUC approval of each project-specific protocol submission or amendment must be readily identifiable and amenable to tracking.

**7. May a former employee or former student of our institution be considered for appointment to our IACUC as a nonaffiliated member?**

PHS *Policy* (IV.A.3.b.4.) defines the nonaffiliated member as an "individual who is not affiliated with the institution in any way other than as a member of the IACUC, and is not a member of the immediate family of a person who is affiliated with the institution," and the USDA's Animal Welfare Regulations expect the individual to "provide representation for the general community interest[34]." The *Guide*[3], which calls this person the "public member," requires additionally that the individual not be a current laboratory animal user. Regarding the service of a former employee in the capacity of a nonaffiliated member, the appointing official would have to receive assurance that the person is not in any way conflicted or beholden to the institution[35]. If there are no discernable ties or ongoing affiliation with the institution, then it would be permissible to consider appointment of the former employee or former student to the IACUC. It is important for officials who appoint IACUC members to determine whether real or perceived conflicts of interest exist and make the appropriate choices to avoid criticism about the institution's or the Committee's integrity. Choosing an individual who is unambiguously 'nonaffiliated' is the best way to fulfill the letter and the spirit of this provision.

**8. Our IACUC has encountered a problem with investigators who do not submit their protocols for review in time to gain approval before the three-year expiration date. Is it permissible to grant an administrative extension of IACUC approval so as to avoid expiration?**

No. For PHS purposes, IACUC review following the provisions at IV.C.2. of the PHS *Policy* must be accomplished at least once every three years[1]. The IACUC may not extend the three-year approval by any means other than IACUC review and approval using the procedures of IV.C.2. When IACUC approval expires, it is no longer valid. Continuation of animal activities beyond the expiration is a serious and reportable violation of PHS *Policy*.

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