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*Note: Text has been edited for clarity.*

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## **Significant Changes to Animal Activities**

### *Speakers:*

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Jerry Collins, PhD, Yale University

Betty Goldentyer, DVM, USDA, APHIS, AC

Mary Lou James, BS, IACUC 101 Series

Cynthia Gillett, DVM, University of Minnesota

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[https://www.youtube.com/watch?v=XGCd30x\\_gQw](https://www.youtube.com/watch?v=XGCd30x_gQw) (YouTube).

Slide 1 (Guidance on Significant Changes to Animal Activities NOT-OD-14-126)

>>*Silk*: Hello. I am Susan Silk, the Director of Policy and Education at the NIH Office of Laboratory Animal Welfare. Today, August 21, 2014, [Guide Notice was released on August 26, 2014] NIH released Guide Notice [NOT-OD-14-126](#), Significant Changes to Animal Activities. I have invited several of your colleagues and a representative from USDA to join me online to discuss NOT-OD-14-126. This guidance will provide increased flexibility in how IACUCs handle significant changes to previously approved animal activities. The panel's contribution to this webinar will be to help me clarify OLAW's and USDA's expectations and to help each IACUC understand the guidance, and effectively use the flexibility that it provides.

The panel includes experts from various parts of the animal care and use community. They were selected to represent the interests of the individuals that work together to conduct animal activities in compliance with the PHS Policy and the Animal Welfare Act and Regulations.

Our panel includes George Babcock, Jerry Collins, Betty Goldentyer, Mary Lou James and Cyd Gillett.

George Babcock, PhD, is professor of immunology at the University of Cincinnati where he is Chair of the IACUC. George also serves as moderator in OLAW's popular online seminar series.

Jerry Collins, PhD, is professor emeritus of anesthesiology at Yale University where he served as the IACUC Chair from 1997 to 2008. I'm delighted he is with us today to share the wisdom he accumulated during his many years of service.

Jerry and George were invited to participate in our panel because they can analyze this significant change guidance from the perspective of both principal investigators and experienced IACUC Chairs.

Betty Goldentyer, DVM, is the regional director of Animal Care for the Eastern Region of the Animal and Plant Health Inspection Service, which is a part of the United States Department of Agriculture [USDA]. Betty will provide the USDA perspective on this guidance and help us to understand how the USDA Veterinary Medical Officers (VMO) will interpret the guidance.

Mary Lou James is a St. Louis based independent consultant in animal program operations and regulatory compliance. She is also a founder and the president of the IACUC 101 Series, the non-profit organization responsible for the IACUC training of so many of us. Lou was selected for this panel because of the breadth and depth of her knowledge assisting academic, commercial, and government sector organizations in improving their animal care and use programs. She will specifically attend to the impact of this guidance on IACUC administrators.

And finally I invited Cyd Gillett, DVM, to be member of our panel. Cyd is the director of animal program operations at the University of Minnesota. She will represent the perspective of an attending veterinarian, an IACUC member, and the director of a large, diverse animal care and use program at a public university.

On the screen you see **Guidance on Significant Changes to Animal Activities**. I will read each paragraph of the guidance, line-by-line, comment on the guidance and then our panelists will discuss the content. Let's start with the background paragraph.

Slide 2 (NOT-OD-14-126: Background)

**The PHS Policy on Humane Care and Use of Laboratory Animals (Policy) (IV.C.1.) and Animal Welfare Regulations ([9CFR 2.31 \(d\) \(1\) \(i\)- \(iv\)](#)) define the responsibilities of the IACUC regarding review and approval of proposed significant changes to animal activities. Changes to approved**

research projects must be conducted in accordance with the institution's Assurance, the United States Department of Agriculture (USDA) Animal Welfare Act and Animal Welfare Regulations and must be consistent with the [Guide](#) unless an acceptable justification for a departure is presented. Additionally, IACUCs are responsible for assuring that the changes to approved animal activities meet the requirements described in the PHS Policy [IV.C.1.a.-g.](#)

In this paragraph, OLAW reminds us that changes to previously approved animal activities must be made according to the appropriate guidance and regulation; that is, the institution's PHS Assurance, the PHS Policy, the *Guide for the Care and Use of Laboratory Animals*, and the USDA Animal Welfare Regulations. What is the panel's reaction?

>>*James*: So, Betty, does this mean that USDA has agreed to this guidance and it applies to both PHS Assured institutions as well as USDA regulated ones as well?

>>*Goldentyer*: Yes, Lou, USDA is in agreement.

>>*Silk*: The IACUC has the authority and responsibility to approve significant changes to proposed animal activities. This new guidance establishes ways that an IACUC can use preapproved procedures that may be incorporated into research projects after initial animal activity approval, sometimes referred to as "protocol" approval.

>>*Collins*: So Susan, it sounds to me as if you are saying that this will now make it possible for some IACUC-approved procedures to be incorporated into research projects after the initial protocol review without the need for full committee or designated member review of a modification.

>>*Silk*: That's right Jerry. That's the big overview. And there are some important conditions and nuances that we will discuss during this webinar. The background goes on to say,

Slide 3 (Background)

**IACUC approval of proposed animal activities or significant changes to previously approved animal activities is granted after full committee review (FCR) or designated member review (DMR). Additionally, institutions may establish and IACUCs may approve policies (e.g., guidance documents, standard operating procedures, drug formularies) for the conduct of animal activities. These policies must be reviewed by the IACUC**

**at appropriate intervals of no less than once every three years to ensure they are appropriate and accurate.**

This paragraph reminds us that significant changes must be reviewed and approved by the IACUC. The next sentence is very important for understanding the rest of the guidance. It says, **additionally, institutions may establish, and IACUCs may approve policies for the conduct of animal activities.** With this guidance, OLAW and USDA are offering IACUCs a new method for review and approval of significant changes to previously approved animal activities. And that new method is by using IACUC-reviewed and -approved policies. The guidance goes on to define what we mean by policies, that is policies with a small "p." We mean guidance documents, standard operating procedures and drug formularies. And it mentions that these policies must be reviewed periodically to ensure that they are appropriate and accurate. Does the panel have any comments on this paragraph?

>>*Collins*: Susan, what do you mean by IACUC-approved policies?

>>*Silk*: By IACUC-approved policies, OLAW and USDA mean that the policies must be adopted by a formal action of the IACUC. I'll define that further. Formal action of the IACUC falls into two categories. The first category is review and approval by full committee review (FCR) or designated member review (DMR). The second is by polling the IACUC. Polling of the IACUC could be conducted in a number of ways. It could be done by telephone calls or email. Or, it could be done by posting the issue in an electronic format and having the IACUC members indicate their preferences there.

>>*Collins*: So, something like SharePoint could be used?

>>*Silk*: Yes, Jerry. Of course that's just one electronic format. Others would be acceptable, too. But it's a good example. The important point is that the members of the IACUC would be aware of the policies and accountable for the policies.

>>*Collins*: Susan, do the IACUC members have to agree unanimously to approve a policy? Or is acceptance by a quorum of the members sufficient?

>>*Silk*: Jerry, that will be up to the individual IACUC to determine. The IACUC may do what works with their business practices and the way they manage their PHS Assured animal care and use program. Acceptance by a quorum of members would be sufficient to meet OLAW's expectations.

>>*Collins*: I think this is a good opportunity to clarify what USDA and OLAW expect regarding review of SOPs. It appears we can reconcile past guidance with what both

agencies expect now regarding frequency of review of policies. Today you have defined policies with a small "p" as institutionally-developed and IACUC-approved SOP's, guidance documents and drug formularies.

>>*Silk*: That's a good point, Jerry. Yes, we are using the term "policies" in this discussion to refer to institutionally-developed and IACUC-approved SOP's, guidance documents and drug formularies. OLAW expects these policies, to be reviewed at least once every 3 years.

>>*James*: Betty, does the USDA agree to a review of policies at least every 3 years?

>>*Goldentyer*: Yes, USDA agrees that it is ok to review certain policies every 3 years. We would expect policies to be reviewed at least every 3 years. Some policies may have to be reviewed more frequently. In that, USDA is consistent with OLAW. The USDA expects the IACUC to determine a schedule of review that is appropriate and then to conduct review according to that schedule.

>>*James*: So, Betty, how does that fit in with USDA's requirement for continual review at least annually, better known as annual review?

>>*Goldentyer*: Section 2.31(d) (5) states that the IACUC shall conduct continuing reviews of activities at appropriate intervals but not less than annually. During that annual review, USDA expects the IACUC to be reviewing any changes to the protocol, regardless of how those changes have been incorporated into the activity.

>>*James*: So in summary, USDA expects protocols will be reviewed annually, but the policies must be reviewed at intervals of no less than every 3 years.

>>*Goldentyer*: Yes, that's correct.

>>*James*: Thank you.

>>*Collins*: In some cases, the IACUC may wish to or may really need to review its policies more frequently, however. For example, a policy on analgesics may define specific drugs but it will need to be changed as more efficacious drugs become the standard of care. It would be inappropriate to wait for 3 years to add something that should be used at the present time.

>>*Gillett*: Susan, is there a required format for the review of policies by the IACUC? For example, does it have to be done at a convened meeting of the IACUC? Or during program review?

>>*Silk*: Cyd, it would be up to the IACUC to make the determination as to when and how they want to conduct the review.

>>*Gillett*: Is there a difference between the method of IACUC review and approval of the initial policy or guidance and the subsequent re-review of a policy that the IACUC previously approved?

>>*Silk*: Approval must be done by a formal action of the IACUC. It is up to the IACUC to determine their practices regarding the review of policies.

>>*Gillett*: So, initial approval does not require FCR or DMR? And neither does the subsequent re-review?

>>*Goldentyer*: That's correct. It remains the responsibility of the IACUC to make sure they are aware of the policies, and that they are in agreement with the policies, and document their acceptance of them.

>>*James*: Can the IACUC change its policy and schedule for the method and timing of the review?

>>*Silk*: Of course they can, Lou. These issues will be determined by the IACUC. I fully expect that policies will change as IACUCs learn to use the guidance we are discussing today and they will change and improve their business practices in ways that benefit the animals, the researchers and the science.

>>*James*: Cyd, what are "drug formularies"?

>>*Gillett*: Drug formularies are lists of drugs that are created and used in a variety of ways. Some drug formularies are general guidance documents, listing acceptable uses, dosages, and routes of administration of a wide variety of drugs that may be administered to animals. In this guidance, the term "drug formularies" refers to specific IACUC-approved and -reviewed drug regimens that investigators can refer to in their protocols and indicate compliance with.

Slide 4 (Significant Changes to Animal Activities Previously Approved by the IACUC)

>>*Silk*: Now, we come to the new material in the guidance: The next paragraphs are under the heading: **Significant Changes to Animal Activities Previously Approved by the IACUC**. This paragraph tells us that,

**The IACUC has some discretion to use IACUC-reviewed and -approved policies to define what it considers a significant change, or to establish a**

**mechanism for determining significance on a case-by-case basis in accordance with the PHS Policy [IV.C.1.a.-g.](#) It is the IACUC's responsibility to clearly define and communicate its policy for determining significance to investigators.**

This paragraph explains that the IACUC may apply IACUC-reviewed and -approved policies to significant changes. It also suggests that the IACUC may develop a policy describing the parameters that it uses to determine significance on a case-by-case basis. The rest of the paragraph explains in more detail what factors the IACUC must consider when applying its policies to significant changes or when defining the parameters it will use to determine significance. And lastly, the paragraph directs the IACUC to inform investigators about these policies in a way that is convenient for them and easier for them to understand. Panel?

>>*Collins*: Susan, can the IACUC redefine items that OLAW has defined as significant? That is, can the IACUC define any of these items as "not significant"?

>>*Silk*: No, Jerry. OLAW has determined this list of significant changes according to the PHS Policy. One of OLAW's jobs – its authority – is to advise awardee institutions concerning the implementation of the PHS Policy. That is section [V.A.3.](#) of the Policy.

>>*Collins*: Then what does "determine significance on a case-by-case basis" mean?

>>*Silk*: It means that if the IACUC wants to, it can consider each individual situation as it comes up and not develop policies, including SOPs, guidance documents and drug formularies. However, the determination reached in each individual situation must be done in compliance with OLAW's interpretation of the PHS Policy with regard to significant changes and other changes. That is how IACUCs have handled requests for changes in the past. They may continue to do it this way if they wish.

>>*Collins*: So Susan, it seems to me that the definition of significant change has not been altered but rather the IACUC has been given authority to pre-approve some activities that are significant that the investigator did not anticipate when the experiment was designed and the protocol was approved.

>>*Silk*: Yes, Jerry, that is correct. The definition of significant change has not changed. Let's see if I understand the second part of what you said. You're talking about a situation in which an investigator writes the procedures they expect to perform in the protocol and the IACUC approves the protocol. Then, as the investigator is conducting the experiment, he or she realizes that there is a better

way to do the procedure. OLAW is saying that if the IACUC has an approved policy in place specifying that they approve changing from the method that was previously approved by the IACUC to the new method that the investigator wants to use – that change would be permitted within some limits that we will discuss in the next section of the guidance.

>>*Collins*: I know all of us on this panel have been frustrated by PIs describing, or IACUCs requiring, narrow ranges for procedures or even exact values in protocols. For example, stating that 1 mg of a drug will be given rather than describing an appropriate range such as 0.2 to 4.0 mg. Clearly the range must be based on accepted standards but by using a reasonable range, one avoids the need to make frequent modifications to a protocol. It seems to me that the new guidance empowers an IACUC to establish acceptable ranges that may be applied to a project without having to undergo the modification approval process. Susan, is that correct?

>>*Silk*: Yes, Jerry, it is. The newly requested procedure must be included in the policy that has been approved by the IACUC. That approval process does not have to occur after it is determined that the change is needed. The IACUC can approve the policy before this specific instance of the change is needed.

>>*Gillett*: Susan, does OLAW have expectations for how the IACUC communicates its policy for determining significance to investigators? Can it be done by posting the policy on the IACUC website? Can it be done by an email listserv communication? Or by providing a handout to the investigators? Or during post approval monitoring visits?

>>*Silk*: Well, Cyd, OLAW does not have specific expectations about how the IACUC communicates its policies. Our expectation is that your communication will be clear and easily accessible to the investigators. Whatever works within your institution will be just fine with OLAW.

>>*Collins*: I'd like to change the topic from communicating with the investigators to the issue of documenting the change that is being made. I believe a best practice will be for each institution to develop a mechanism by which the change is incorporated into the active protocol so others can see that the new broader approval is OK.

>>*Silk*: Yes, Jerry, I agree. OLAW and USDA want the institution to document the change, but we are not being prescriptive about how that documentation is to be done. It's important that the change be recorded, somehow, in the protocol. OLAW and USDA expect the institution to develop a method that works for its program

and with the IACUC's business practices to make sure the change is recorded and available to those who need the information.

>>*James*: It is also important for the change to be documented for IACUC members and other oversight personnel who are tasked with ensuring that a protocol is being conducted as approved, such as your post approval monitors, your veterinary staff and animal care personnel. Otherwise it may appear that the PI is deviating from the approved protocol.

>>*Goldentyer*: That's exactly right, Lou. USDA will expect that changes to the activities are reflected during the annual review process so that the IACUC and the USDA inspector have a complete written description of the use of the animal.

>>*Silk*: Now, returning to the guidance document. The next paragraph defines what a significant change is. It says,

Slide 5 (Significant Changes to Animal Activities Previously Approved by the IACUC)  
**In brief, significant changes include changes that have, or have the potential to have, a negative impact on animal welfare (see paragraph 1., below). In addition, some activities that may not have a direct impact on animal welfare are also considered to be significant (see paragraphs 2. and 3., below).**

>>*Gillett*: Susan, can you give some examples of activities that may not have a direct impact on animal welfare but would still be considered to be significant?

>>*Silk*: Sure, Cyd, a change from one method of administration of an infectious agent to another may not increase risk to the animals but it may increase risk to personnel. For example, the change to administer a pathogen by inhalation instead of injection. The animal might receive a lower dose of the infectious agent with this change, but the IACUC must ensure that risk assessment and training of personnel have occurred.

Slide 6 (Significant Changes to Animal Activities Previously Approved by the IACUC)  
In the next paragraph, OLAW describes why we have issued this guidance. We then go on to describe the specific ways in which IACUCs may apply this guidance. The paragraph says,

**In support of the use of performance standards and professional judgment and to reduce regulatory burden, IACUC-reviewed and -approved policies (e.g., guidance documents, standard operating procedures, drug formularies) for the conduct of animal activities may be used for the**

**administrative handling of some significant changes according to the following considerations:**

Before we discuss the considerations, I want to emphasize an important idea in the guidance. It is this, **“IACUC-reviewed and -approved policies for the conduct of animal activities may be used for the administrative handling of some significant changes.”** Later in this webinar, I will clarify what we mean by administrative handling, because this has a very specific meaning in this context. But now I’d like to discuss the specifics of this guidance so that you will understand what IACUCs must consider to take advantage of the flexibility offered by the guidance.

Slide 7 (Paragraph 1.)

>>*Silk*: OK, on to paragraph 1. Paragraph 1. addresses the significant changes that must be reviewed and approved by the IACUC. This was true before this guidance was issued and it is still true under the new guidance. Paragraph 1. says,

- 1. Significant changes described in 1.a.-g., below, must be approved by one of the valid IACUC approval methods described in the PHS Policy [IV.C.2.](#), that is FCR or DMR, including changes:**
  - a. from nonsurvival to survival surgery;**
  - b. resulting in greater pain, distress, or degree of invasiveness;**
  - c. in housing and or use of animals in a location that is not part of the animal program overseen by the IACUC;**
  - d. in species;**
  - e. in study objectives;**
  - f. in Principal Investigator (PI); and**
  - g. that impact personnel safety.**

Does the panel have questions about this paragraph? These are not changed from previous policy.

>>*James*: Susan, I have a question: does 1.a. which says “from nonsurvival to survival surgery” imply that a change from survival to nonsurvival surgery is NOT a significant change and therefore does NOT have to be reviewed?

>>*Silk*: No, Lou, it only means exactly what it says. That the IACUC may NOT have a policy that allows the investigator to change from nonsurvival to survival surgery. We will discuss a change from survival to nonsurvival surgery when we discuss paragraph 2. The significant changes listed in paragraph 1.a. through 1.g. must go to the IACUC for review by FCR or DMR.

>>*James*: OK, so that means that the policies that address significance may not address the issues in 1.a. through 1.g. These must be reviewed and approved by FCR or DMR.

>>*Silk*: Yes, Lou that is correct.

Slide 8 (Paragraph 2.)

Moving on, I'm sure you're all waiting to hear about significant changes that may be handled administratively with veterinary consultation. Paragraph 2. states,

- 2. The specific significant changes described in 2.a.-c., below, may be handled administratively according to IACUC-reviewed and -approved policies in consultation with a veterinarian authorized by the IACUC. The veterinarian is not conducting DMR, but is serving as a subject matter expert to verify that compliance with the IACUC-reviewed and -approved policy is appropriate for the animals in this circumstance. Consultation with the veterinarian must be documented. The veterinarian may refer any 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. This includes changes in:**
- a. anesthesia, analgesia, sedation, or experimental substances;**
  - b. euthanasia to any method approved in the [AVMA Guidelines for the Euthanasia of Animals](#); and**
  - c. duration, frequency, type or number of procedures performed on an animal.**

Notice that OLAW is using the term "administrative handling" to apply to consultation and verification by the veterinarian. Because these are all changes that potentially could involve pain and distress to the animal, the expertise of the veterinarian is required.

>>*Collins*: Susan, does this mean that the IACUC staff or administrator may not verify these changes.

>>*Silk*: Yes, Jerry, that's exactly what it means. The expertise of the veterinarian is required here. Only the veterinarian may verify the changes listed in 2.a. through c.

>>*James*: So, Susan, I am homing in on that word "verify" in the sentence that states that the vet is not performing DMR but rather serves as a subject matter expert to VERIFY that compliance with the IACUC-approved policy is appropriate for the animals in this circumstance. Verify seems to be a key word that distinguishes the vet's actions from DMR. Rather than reviewing and approving an amendment,

the vet is verifying or confirming that the official IACUC policies support the change being requested as appropriate. Is that correct?

>>*Silk*: That's correct, Lou.

>>*James*: And, if the vet is uncertain or does not feel the change is consistent with the existing policy, or maybe is concerned that the change in this specific case may negatively impact animal welfare or the science, they should refer it for FCR or DMR?

>>*Silk*: Absolutely correct. If the change is consistent with the existing policy, but not the best choice for this animal or in this situation, the veterinarian would have the responsibility to refer the change for IACUC review. Or the veterinarian could suggest a different change that is consistent with the existing policy and OK for the animals and the science.

>>*Gillett*: Susan, does the veterinarian who is verifying the change have to be the attending vet (AV)?

>>*Silk*: No, Cyd. The IACUC can identify veterinarians that may make this determination for the IACUC. Remember that the IACUC may use the services of consultants. The veterinarian does not have to be the AV, nor does the veterinarian have to be a member of the IACUC. A staff veterinarian can serve as an IACUC consultant in this situation. The important thing is that the IACUC is confident that the vet, in addition to being knowledgeable about the procedures and substances and the animals, is also knowledgeable about the policies and expectations of the IACUC.

>>*Gillett*: Does it have to be just one designated veterinarian?

>>*Silk*: Oh no. It can be as many as the IACUC wants. The important limitation is that each one be knowledgeable and qualified in the way that I explained earlier.

>>*Gillett*: What would be a circumstance that a veterinarian would refer for IACUC review? What if the change involves the use of gas anesthesia by a researcher that has not used it before? The veterinarian may wish to have the IACUC review and provide the researcher with expectations regarding personnel training and occupational health and safety. Although, the vet could provide that information as well.

>>*Silk*: Well Cyd, that is a tricky question and the answer is – it depends. The situation is a little bit far down in the weeds for a training webinar, but I think it

could be useful to explain how OLAW would answer that question. If the change to gas anesthesia impacted personnel safety, then the change absolutely would have to go back to the IACUC for FCR or DMR, as required by paragraph 1.g. of this guidance. If the group had not used inhaled anesthesia before and if they were going to get out a brand new machine and set it up and proceed to do the surgery. That would require IACUC review.

But what if the situation was different? If the change to gas anesthesia was requested by a group that routinely uses inhaled anesthesia and is trained and experienced in its use and the surgery will be performed in surgery suite that has a scavenger table already set up and safety tested. Then the veterinarian could verify and approve the change, provided the IACUC has approved the veterinarian to make that judgment.

This raises another question. What if the situation involved a change to a method or procedure that the group was inexperienced with, but the risk was to the animal not to the personnel? In that instance it would be up to the foresight of the IACUC and the good judgment of the veterinarian. If given the authority, the vet could train the personnel, or could refer the team to another component of the program responsible for training, or the vet could refer the situation back to the IACUC for consideration.

>>*Gillett*: OK well here's another situation. If a change in the duration or in the number of procedures in a study is such that the veterinarian thinks it may negatively impact animal welfare, the veterinarian would probably want to refer it to the IACUC for assessment.

>>*Silk*: I think the veterinarian would be right to refer that for IACUC review, Cyd.

>>*Collins*: Susan, what happens if a PI requests a change that is not covered by any existing policies?

>>*Silk*: There are three options, Jerry. One option is for the investigator to submit an amendment to the IACUC for review and approval. This is the way IACUCs have handled significant changes in the past.

A second option is for the IACUC to modify an existing policy to include the requested change according to the IACUC-established mechanisms for doing so.

A third option is for the IACUC to develop a new policy that addresses the requested change, again according to the IACUC-established mechanisms for doing so.

>>*James*: Susan, does this policy now require us to have a written IACUC-approved policy in place for veterinary interventions?

>>*Silk*: Absolutely not, Lou. A veterinarian can and must provide clinical care, as needed. The veterinarian has always had the responsibility to intervene and provide clinical care to relieve pain and distress in, for example, an animal that is undergoing a procedure and needs to have a different dose or a different anesthesia. What is new is that the vet now has the authority to permit the investigator to extend that modification, that significant change in anesthesia, to the other animals in the study without additional IACUC review, provided that the IACUC has a previously approved a written policy in place specifying that the change is acceptable.

>>*Babcock*: Susan, how specific or detailed do these policies really have to be? Can they be written such that the veterinarian can determine the specific changes under a broad umbrella? As an example of this, can the policy list acceptable anesthetics but allow the vet to alter the dosage within a range the veterinarian determines rather than the policy?

>>*Silk*: George, I'm not sure how to answer that because I can imagine many different situations could fall under that very broad hypothetical scenario. I should think that it would be just fine for the IACUC to empower the vet to make decisions regarding dosage of a drug. But I'd like to hear the panels' opinion. Cyd, you are an IACUC member, a vet, and the director of a large program. What is your opinion about George's question?

>>*Gillett*: I think it's a good idea to have a broad policy that allows the veterinarian to use their professional judgment to make that determination within the limits of the established policy.

>>*Collins*: I'd like to make a point, while there is no requirement for a policy allowing veterinary intervention, it is a very good idea for each IACUC to make sure that all investigators are aware that the veterinarians have that authority. Many institutions require emergency contact information from a PI in order to be able to get in touch when veterinary intervention is needed – not to request permission but to inform the PI of what must be done. Part of that process of getting emergency contact information should contain a clear statement about veterinary authority.

>>*Silk*: There is very clear language in the *Guide* about the authority and responsibility of the veterinarian to provide clinical intervention when it is needed. Cyd, could you come up with an example of a situation where veterinary

intervention for a single animal is needed and how this new guidance could be used to benefit the rest of the animals in the experiment?

>>*Gillett*: For example, an investigator is approved in the protocol to administer ibuprofen in the drinking water as analgesia for guinea pigs after surgery to implant osmotic mini-pumps. The veterinarian notes that one guinea pig is not moving or drinking much water during the first few hours after surgery and orders an injectable analgesic to be administered. Under this new guidance, if there is an IACUC-approved policy on the analgesics that can be used in rodents, the veterinarian could verify that a change to add the [post-operative] injectable analgesic would benefit all the guinea pigs who now may have pump implant surgery with ibuprofen on this protocol without requiring the investigator to submit an amendment for FCR or DMR, not just the guinea pig in need of immediate attention. Is that correct?

>>*Silk*: Yes, Cyd, that's a good example.

>>*James*: So Betty, what if the PI was approved to use a USDA-regulated species and never anticipated any pain when the protocol was submitted to the IACUC. The PI assigned all animals to the C pain category. But during the studies, some of the animals do experience pain. The PI contacts the vet to see if he can administer analgesia, not only for the animals in pain, but any subsequent animals on the protocol. For those animals in pain, the vet agrees that the PI should go ahead and administer the analgesia. This is a permitted veterinary intervention. The IACUC has accepted a policy that allows administration of this analgesia at the given dose to alleviate pain in the species being used. Can the vet give the nod to provide analgesia to subsequent animals that have not yet been treated?

>>*Goldentyer*: Yes, Lou, the vet should certainly intervene to assure that analgesics are administered to the animals currently experiencing pain and for those that might subsequently experience pain. However, if the vet and the PI now consider this protocol to include procedures that may cause more than momentary pain or distress, the protocol should go back to the IACUC for review with a search for alternatives to those procedures and include the administration of the appropriate analgesics.

>>*Silk*: OLAW agrees, Betty, this would fall under section 1.b. of our guidance. That is, in this situation, the animal is experiencing greater pain or distress than anticipated or previously approved. So before the analgesic can be administered to the additional animals on the protocol, this would need to go back to the IACUC for review.

>>*Collins*: Susan, I think that this is an excellent example of how an IACUC must think through how this new guidance is used. In this example we are discussing a USDA covered species and a situation in which the pain and distress category may be changed. If that is the case then allowance must be made for the relevant literature search.

>>*Goldentyer*: Yes, Jerry, that is correct.

>>*Gillett*: For example, if my IACUC has approved a species specific list of acceptable anesthesia regimens for major survival surgery or a similar list for minor surgical procedures and the veterinarian recommends using another regimen from the appropriate IACUC-approved list, that would be an administrative change that could be done by consultation with the vet, correct?

>>*Silk*: Your example situation is right but your wording is wrong. I'm glad you said it this way because I think many of us might make this language mistake. You said that this change in anesthetic regimen is an administrative change. It is NOT, NOT, absolutely NOT an administrative change. It is a significant change. OLAW has interpreted the PHS Policy to allow an administrative handling of a certain group of significant changes. The reason that I am being so picky about the language is that I don't want this misuse of the language to lead you into misinterpretation of the guidance leading to a noncompliant situation. Administratively making significant changes would be noncompliance that would have to be reported to OLAW. So please, I don't want anyone to say, "This is just semantics." It is precision with language and I'm being very strict about it to protect you from misunderstanding the guidance.

>>*Gillett*: Thank you for that clarification and I take your point. These are NOT administrative changes. They are significant changes that may be handled administratively provided there is veterinary consultation and verification and the changes are covered by an IACUC-approved policy or policies that is appropriate for the animals and circumstances. Is that right?

>>*Silk*: Absolutely one hundred percent right, Cyd.

>>*Collins*: Susan, is there any expectation from OLAW about the time between verification by a veterinarian and the utilization of the new technique?

>>*Silk*: Jerry, it may be implemented immediately after the veterinarian verifies the change.

>>*Collins*: Susan, could we go back to a question that came up earlier, that is, the question about a change from survival surgery to nonsurvival surgery. OLAW's opinion is that this change falls under section 2.c. of this guidance. A change from survival to nonsurvival surgery is a change in procedure. The IACUC may approve a policy permitting this, but it is a significant change that must be verified by a veterinarian, is that correct?

>> *Silk*: Yes, that's absolutely correct.

>>*James*: So Susan, let me just make a statement here and tell me if I got this correct this time. So a change from survival surgery to nonsurvival surgery is a significant change that can be administratively handled with a veterinary consultation and verification if an appropriate IACUC-approved policy is in place?

>>*Silk*: Yes.

>>*Collins*: We need to emphasize that any change, such as an increase in the dose of anesthesia, analgesia, or sedation, may necessitate additional monitoring beyond that described in the original approved protocol. In addition, there may be new training requirements that must be applied as well.

>>*Babcock*: Jerry, to expand on this a little, if additional procedures are added, these procedures may well require changes in monitoring, too.

>>*Silk*: Yes, George, the IACUC is going to have to write these policies thoughtfully and carefully. Perhaps revised monitoring could be a stipulation in a well-written policy. Verification by the veterinarian will help ensure that the level of care, such as additional monitoring, is adequate. Keep in mind however that OLAW has listed changes resulting in greater pain, distress, or degree of invasiveness as ones that can only be approved by FCR or DMR. So if a requested additional procedure may result in greater pain, distress, or degree of invasiveness, it must go back to the IACUC for FCR or DMR.

>>*Babcock*: Susan, what does verification really mean in this context? To me verification would be a check or safeguard of proposed changes by the PI and covered by the policy. If the policy specifies an acceptable range, would the vet still be able to recommend a specific dose within this range? To me this is more than verification. As an example, the IACUC approves a policy which gives a dose range for a drug of 1 to 10 mg/kg. The PI asks to change the dosage in his or her protocol from 4 to 5 mg/kg. The veterinarian indicates that 6 mg/kg would be better. I assume this is acceptable, so verification really means verification and consultation?

>>*Silk*: Good point, George. Yes, the administrative handling of this significant change would include both veterinary verification and consultation. Remember the guidance states, "The veterinarian is serving as a subject matter expert to verify that compliance with the IACUC-reviewed and -approved policy is appropriate for the animals in this circumstance. Consultation with the veterinarian must be documented."

>>*James*: So Susan, if the change has the potential for pain or distress, the verification would include a veterinary consultation so the vet does retain the authority to recommend a dose within the specified range and in particular in your example since it suggests that the procedure has the potential to be painful or distressful. It may be best if the corresponding IACUC policies reiterate that the vet retains authority to make recommendations within the IACUC-approved policies to ensure minimum pain and distress.

>>*Silk*: Lou, that sounds like it could be a best practice that an institution may want to consider writing into their policy. But I think that level of detail is implied by the guidance, so I don't know that it would have to be specifically written into the policy for the veterinarian to have that authority. The guidance says that the veterinarian must be consulted and has the authority to approve options provided within the ranges specified in the policy. I think individual IACUCs will know their own institution and they will know how much detail will be required in the policies they develop.

Could the panel suggest some other examples of the types of things that would fall under paragraphs 2. a., b., and c.?

>>*Collins*: Susan, I have one. An investigator is approved in a protocol to restrain an animal for 30 minutes. The IACUC has a policy that this species may be restrained for up to 45 minutes. After beginning the study, the PI realizes that there is a need to restrain the animal for 40 minutes to collect the needed data. Will the veterinarian be able to verify that the change to a longer period of restraint is covered by the IACUC-approved policy and therefore instruct the PI to proceed with the requested change?

>>*Silk*: Yes, Jerry, the veterinarian may verify that the change is appropriate and is within the IACUC's policy. And the PI may proceed with that change after the veterinarian indicates that the change is OK. The veterinarian and the PI must document the change according to the procedures that the institution has established.

>>*Collins*: Susan, here's another possible example. What about a psychology student who has been approved to use 3 different means of inducing stress in mice. The IACUC has approved 7 different methods, and has stipulated that only one method is to be applied to any one animal. The student needs to use one of the approved methods on that IACUC-approved list but one that was not included in the initial protocol. Here again will the veterinarian be able to verify that the change to a different method is covered by the IACUC-approved policy and is appropriate for this situation and therefore instruct the PI to proceed with the requested change?

>>*Silk*: Yes, Jerry.

>>*James*: Susan, what if the proposed method is not one of the methods included in the IACUC policy?

>>*Silk*: Well, Lou, as I said before, there are 3 options. One option is for the investigator to submit an amendment to the IACUC for review and approval. This is the way we have handled significant changes in the past.

A second option is for the IACUC to modify the existing policy to include the requested change according to the method that the IACUC has established for changing policies.

A third option is to develop a new policy that addresses the change in accordance with the IACUCs policy for developing and accepting policies.

>>*Gillett*: Another example, an investigator has protocol approval to draw 10 cc of blood from an adult rabbit once a week for 3 weeks. The IACUC policy on blood collection allows for up to 0.5% of the body weight to be withdrawn when done on a weekly basis. That would be 15 cc per week for this 3 kg rabbit. The PI now realizes that he needs 15 cc per week for 4 weeks.

>>*Babcock*: Cyd, I think that is another great example of how the new guidance will allow an immediate change in the procedure without the time delay associated with submitting an amendment to a protocol and waiting for the IACUC to approve it.

>>*Collins*: OK. Here's an example for those of you that have attended IACUC 201. I write a protocol and in my protocol, I request up to 6 blood draws but the IACUC has a policy that allows up to 10, so if I find that I need to do 8, I can submit my change to the vet and confirm that in my case, it will not endanger the animals. Since the IACUC already approved up to 10, I do not need to seek additional

confirmation of that approval by the IACUC. The veterinarian is verifying, for the IACUC, that their policy is being applied appropriately.

>>*James*: So Jerry, you mean like on the Friday after Thanksgiving and a technician drops a test tube of blood and then the technician needs to do an additional blood draw on a group of rabbits?

>>*Babcock*: Lou, exactly. The vet on-call could authorize the additional blood draw by phone from home, since the additional blood draw is within the range approved in the IACUC policy and the veterinarian is familiar with the training and experience of the technician.

>>*James*: Good, that's definitely going to please our PIs.

>>*Gillett*: And the vet on-call who doesn't have to give the PI bad news about not being allowed to make that kind of change.

>>*Collins*: Am I correct in assuming that the IACUC policy should identify the veterinarians who have the authority to verify the change?

>>*Silk*: Yes.

>>*Babcock*: What would the policy actually need to indicate? All veterinarians in laboratory animal medicine? Should it include specific titles, such as attending vet or clinical vet, or should it be actual names of the veterinarians who are allowed to do this?

>>*Silk*: Well, George, the IACUC should determine that. I think it would be determined by the way the organization runs its program. It could be done by title, by name, or by function, such as the on-call vet.

>>*Babcock*: Susan, what does consultation with the veterinarian actually mean? You just said this could be done by a phone call. Is that really OK? Or does it mean the PI must meet with the vet in real time? Or could they communicate by email or text or some other electronic means?

>>*Silk*: George, all of those could be acceptable. It is up to the IACUC and the veterinarian to establish the most effective way to take advantage of the flexibility offered by this guidance.

>>*Gillett*: Susan, what are acceptable methods by which the consultation with the veterinarian should be documented? Can the veterinary consultation be maintained

in an administrative file? Can it be documented in the meeting minutes? Can it be added as an attachment or note within the body of the protocols to which the change applies? Other ways?

>>*Silk*: Cyd, this comes back to Jerry's best practice idea. Documentation is required. We want to make sure that the change is available to the team working under the protocol and to the PI designing the next experiment or writing the next protocol. And also to the USDA VMO making an inspection visit. But keep in mind, we are doing this to reduce regulatory burden that we know is making it difficult for investigators to conduct their experiments and for IACUCs to meet their obligations. So OLAW and USDA want institutions to design a way to document the change that records the change in a useful way without being burdensome.

>>*Gillett*: That sounds good. Susan, what is meant by the phrase "changes in euthanasia to any method approved in the AVMA Guidelines for the Euthanasia of Animals"? Are there changes to euthanasia methods that cannot be handled administratively according to IACUC-approved policies?

>>*Silk*: Yes, let me explain what OLAW and USDA mean by that. As you know, investigators are required to use a euthanasia method that has been recommended in the AVMA Guidelines. However, if they need to use a method that is not recommended in the Guidelines for a scientific reason, the IACUC may approve that scientific justification using FCR or DMR. After approval, the investigator may then use that scientifically justified method. What OLAW and USDA are saying is that the IACUC may have a policy to allow a change to an AVMA recommended method whether the original method was recommended in the AVMA Guidelines or was a scientifically justified IACUC-approved method. However, the IACUC may not have a policy that allows the veterinarian to approve a change to a method that is not recommended in the AVMA Guidelines.

>>*Gillett*: So what I think I hear you saying is that changes involving euthanasia methods that are not approved in the AVMA Guidelines may not be handled administratively, but must instead be reviewed by either FCR or DMR.

>>*Silk*: Yes, that's what I'm saying Cyd. It's a one-way street. The vet may, on the IACUC's behalf, administratively handle a change FROM a scientifically justified, IACUC-approved euthanasia method TO any AVMA acceptable method. However it is not OK if the investigator wants to change from an AVMA acceptable euthanasia method to one that is not acceptable in the AVMA Guidelines. That significant change must be reviewed and approved by the IACUC and may not be handled administratively by the vet.

>>*Babcock*: Susan, I'd like to look through the eyes of a PI. If it is in an IACUC-approved euthanasia policy and it follows the AVMA Guidelines, why do I need consultation from the veterinarian?

>>*Silk*: Well, George, to ensure that there are no unusual or special circumstances with that particular research situation. Or perhaps the method is acceptable under the AVMA Guidelines, but the team is not trained or skilled in the use of that method. Please notice that all the situations in which OLAW and USDA require veterinary consultation involve procedures being done to the animals. These are situations where we think there is potential for pain and distress to the animal and we have required this consultation as a safeguard to protect the animal from potential pain and distress.

>>*Gillett*: Susan, what if the proposed euthanasia method is considered acceptable with conditions by the AVMA Guidelines?

>>*Silk*: Using a method that is acceptable with conditions is permitted as long as the conditions are met. So the IACUC-approved policy may include all of the methods that the AVMA Guidelines considers acceptable, including those that are acceptable with conditions. Determining that the required conditions are met would be a part of the verification by the veterinarian in the administrative handling of this significant change.

Incidentally, the IACUC policy does not have to permit administrative handling with vet consultation and verification of all the euthanasia methods permitted in the AVMA Guidelines. They may select a subset of the AVMA-approved methods if they wish.

OK, does anybody have any more comments or questions about veterinary consultation and verification of significant changes that can be handled administratively?

>>*James*: I do, Susan. So if a PI requests a change to an AVMA acceptable method of euthanasia but the veterinarian is uncertain that the staff are trained and qualified to perform that method of euthanasia, can the vet first ask the IACUC administrative staff to confirm training and qualification or is the vet obligated to defer the request for change to the IACUC for review and approval?

>>*Silk*: Lou, it is up to the IACUC and to the institution. The vet could make the decision, or could refer to the IACUC or the IACUC's designee.

Slide 9 (Paragraph 3.)

Moving on, there is also a significant change that may be handled administratively without consultation or verification. Paragraph 3. states,

**3. A significant change that may be handled administratively according to an existing IACUC-reviewed and -approved policy without additional consultation or notification is an increase in previously approved animal numbers (PHS Policy [IV.D.1.a.](#)).**

>>*Gillett*: Are there any restrictions on what parameters the IACUC may include in an administrative policy regarding increases in previously approved animal numbers? Previously OLAW allowed a 10% increase in approved rodent numbers; is that percentage the maximum that may be approved administratively? Are USDA regulated species included in this guidance?

>>*Silk*: No, Cyd, 10% is not the maximum increase permitted. The PHS Policy and the AWA Regs specify that the investigator must provide the approximate number of animals to be used to the IACUC for review and approval. And that is being done when the initial protocol is reviewed and approved. OLAW and USDA have now agreed to allow the IACUC to use the flexibility inherent in the term "approximate number" to develop policies that specify ranges the IACUC finds acceptable.

>>*Goldentyer*: As a reminder, the Animal Welfare Act Regulations (Section 2.31(e)(2)) require that the proposal, or a significant change in the proposal, contain a rationale for involving animals, the appropriateness of the species, and the numbers of animals to be used. The IACUC will want to be sure that the rationale for the numbers of animals to be used supports the number, range or percent that is being requested.

>>*Babcock*: So, Betty, is there required written documentation for a change in animal numbers under this policy?

>>*Goldentyer*: The policies that specify the acceptable range for animals used must be documented, yes. And as the numbers change those changes may need to be supported by a revision of the rationale for the numbers of animals used, which should then be documented and included in the annual protocol review.

>>*Babcock*: So Betty, looking at it from a PI [perspective], can the IACUC make a policy that allows me to order any number of animals as long as I keep my group sizes as stated in my protocol?

>>*Silk*: If it's okay, I'll take this one. The IACUC must review and approve the number of animals that the PI provides in the original protocol. Remember that in section [IV.D.1.a.](#), the PHS Policy states that the investigator must provide the "approximate number of animals to be used." In [IV.D.1.b.](#) it goes on to require the investigator to provide "the rationale for involving animals, and for the appropriateness of the species and numbers used." This new guidance gives the IACUC the authority to determine how many additional animals can be added to the protocol within the limit of the phrase of "approximate number of animals to be used." That is not a license to use any number of animals at all.

>>*Goldentyer*: And USDA is in agreement with that.

>>*Babcock*: So it really behooves the IACUCs to write policies that are carefully thought out and address the scenarios they anticipate.

>>*Silk*: Yes. The IACUC may develop a policy to enable investigators to deviate from the number previously approved. It will be up to the IACUC to determine whether that is a percentage, an exact number, a relative number, or to allow no deviation at all. Their policy may be species specific, allowing a certain amount of flexibility with one species and a different amount for another. It might be a best practice to include language addressing a change in group size. It will be up to your IACUC to determine what is in the best interest of the animals, the science, and the researcher. Many institutions have integrated the number of animals permitted into their ordering procedures, their space allotment procedures, even into the charges for their animal space. The policies that IACUCs develops around this issue are likely to be very specific to the practices at their individual institutions.

>>*Babcock*: Susan, would OLAW expect the PI to include a justification for a change in animal numbers in their request?

>>*Silk*: Well, George, as Betty previously stated, OLAW, like USDA, expects that an explanation from the PI for the change in numbers may be needed, as determined by the IACUC's policy. The IACUC policy would have to be carefully thought out. If the animals are needed because of unexpected deaths or an adverse event, the IACUC should be informed. I will be interested to see what kinds of policies the IACUCs develop.

Slide 10 (Other Changes: Paragraph 4.)

Moving on, in paragraphs 4. and 5., we discuss other changes. That is changes that are not considered significant. Paragraph 4. states,

**4. Changes that may be handled administratively without IACUC-approved policies, consultations, or notifications include:**

- a. correction of typographical errors;
- b. correction of grammar;
- c. contact information updates; and
- d. change in personnel, other than the PI. (There must be an administrative review to ensure that all such personnel are appropriately identified, adequately trained and qualified, enrolled in occupational health and safety programs, and meet other criteria as required by the IACUC.)

>>*James*: Okay, Susan, this one is important to me. Does this mean IACUC administrators or IACUC designees may make corrections and may changes in personnel other than the PI without informing the IACUC of those changes?

>>*Silk*: Yes, Lou, that is exactly what we are saying. Administrative review does not require review and approval by the IACUC in this circumstance. And that is not new guidance. This has been permitted for quite some time.

Slide 11 (Other Changes: Paragraph 5.)

So now we'll move on to Paragraph 5., it says,

**5. Investigators may use fewer animals than approved. This does not require IACUC approval, notification, consultation, or administrative handling.**

This means that the PI does not have to inform anyone if he or she uses fewer animals than approved.

>>*Babcock*: Susan, I think the PI should probably be reminded that although they may use fewer total animals, they still should keep their group sizes large enough to obtain statistical significance.

>>*Silk*: That's a good point, George, and I think that is the kind of idea that will come up in discussion when an IACUC is developing a policy or reviewing a policy.

Slide 12 (USDA Concordance)

Now we come to the final paragraph; it repeats that USDA has reviewed OLAW's policy on significant changes and concurs with the guidance.

Does the panel have other comments about this guidance now that we have read and discussed the entire Guide Notice?

>>*Collins*: This new guidance requires that we rethink how an IACUC may approach approval of animal activities and because of that there are some key ideas that we can summarize that will help us better understand the guidance.

Investigators and IACUCs have always been able to describe animal activities in broad terms that, while appropriate, do not impose unnecessary limits on what can be approved.

>>*James*: So I have a comment. Couldn't investigators just avoid having to make a number of significant changes by incorporating reasonable and justified flexibility into their protocol on the front-end? And shouldn't IACUC's help investigators by encouraging flexibility in their protocols and pointing out when a PI may be submitting a protocol that is just too rigid? I have seen IACUCs push investigators into providing so many details and specifics in their written descriptions or in flow charts, or even both, that it sets investigators up for either noncompliance or for being confronted with the need for an emergency amendment approval.

>>*Silk*: It's a good point, Lou. OLAW has been encouraging investigators to write and IACUCs to approve ranges rather than specific values. One way to think of this current guidance is that OLAW and USDA are now suggesting that the IACUC itself develop appropriate ranges and provide those to investigators in the form of IACUC-approved policies.

>>*Collins*: Mary Lou has raised an important point. Sometimes the IACUC is a source of regulatory burden. Specifically, we sometimes encounter situations where an IACUC has asked for an excessive amount of detail, requiring investigators provide information that is then ignored by the very same committee that made the request. It is important to only request information necessary to reach an informed decision about the appropriateness of the proposed work.

Because this guidance is so important and, at first glance may seem challenging to interpret I would like to restate, yet again, what we are telling folks. OLAW's definition of a significant change has not changed and may not be changed by an IACUC. What this new guidance does is to present an optional efficient way to implement some significant changes.

It is important to understand that an IACUC does not have to take advantage of this new guidance. They may continue to use their current business practices. IACUCs may choose to implement this guidance over time as they determine ways it may improve their programs.

### Slide 13 (Inquiries)

>>*Silk*: I think the community will have lots of questions about this guidance. I want to encourage PHS-Assured institutions to email their questions to OLAW at [olawdpe@mail.nih.gov](mailto:olawdpe@mail.nih.gov). This webinar is recorded and posted on the OLAW Education Resources webpage [[Special Seminars](#)]. We will compile the questions that we receive just after this webinar is posted and attach those questions to the webinar transcript. If you would like your questions to be included in this compilation, please email them to OLAW by October 1, 2014 at [olawdpe@mail.nih.gov](mailto:olawdpe@mail.nih.gov) or you can also use the general OLAW email box [olaw@mail.nih.gov](mailto:olaw@mail.nih.gov). We will post the amendment to the transcript as soon as we get all the questions answered. And if you are reviewing the webinar after October 1, 2014 and have questions, you can also send them to OLAW. We will answer your questions, but may not amend to the transcript.

I have received a very generous offer from the [IACUC Administrators Association](#) (IAA). The IAA sponsors Best Practice Meetings and has developed a website to promote sharing best practices among institutions. The IAA has offered to post policies that IACUCs develop in response to this specific change guidance on their website for the use of the entire community. So as your IACUC develops policies, you can share your policies within the community. And before you get started, you can check the IAA website to see if there is a policy that you can adapt for your institution's use. I'd love to see many of you combine your collective wisdom and experience to develop robust, effective policies. I think it will save time and effort while resulting in better policies. If you want to participate, you can email your policies to [info@IACUCA.org](mailto:info@IACUCA.org). There are other templates and best practices posted on the IAA website that are available to members only. IAA developed this firewall to promote secure discussion and exchange. But these significant change policies will be outside the firewall and will be accessible to everyone. It will be up to the institution to decide if you wish to post your policies under the name of your organization or anonymously.

Now, would anyone like to make any last comments on our discussion today?

>>*Collins*: Susan, it strikes me that this new guidance is an outstanding example of the community working together to enhance science while maintaining a focus on humane animal care. The guidance is a direct result of the comments OLAW received on how the IACUC process could be improved.

>>*Silk*: Yes, Jerry, that is really true. We got good comments from the community and we took those comments seriously. This guidance is the result of a partnership between OLAW, USDA, and the community. I speak for all of the people at OLAW when I say thank you for working with us on this. I also want to thank the panel for

their time and work in preparing this webinar to help all of us understand the guidance.

In closing, I want to comment on the implications of this guidance. The IACUC's mission has not been changed by this new guidance. It encourages IACUCs to provide increased flexibility in their policies regarding significant changes to previously approved animal activities. IACUCs must continue to fulfill their responsibility to oversee the nation's animal programs to ensure the appropriate care and use of animals involved in research, research training, and biological testing activities conducted at their institution. This guidance provides IACUCs increased flexibility in meeting those responsibilities and relies on performance standards that are based on the education and experience of all of you involved in PHS-Assured and USDA-regulated animal care and use programs. If you have questions, write to OLAW, if you have policies, share them through IAA.

>>*Goldentyer*: I'd like to make sure we recognize Susan for making this great webinar happen. We hope that institutions will find this increased flexibility useful. And, Jerry, you get the last word.

>>*Collins*: It is now up to each IACUC to accept the responsibility of implementing this new guidance in a way that maintains compliance with the guidelines and regulations while reducing administrative burden. Thanks to all of you for listening. Goodbye.

## Submitted Questions Not Addressed During the Webinar

### Administrative Handling

**Q1:** Paragraph 3 of [NOT-OD-14-126](#) says, "A significant change that may be handled administratively according to an existing IACUC-reviewed and -approved policy without additional consultation or *notification* is an increase in previously approved animal numbers." Does *notification* refer to notifying the veterinarian or to someone or something else (e.g., protocol office)?

**A1:** The protocol office, IACUC office, IACUC administrator, or other individuals who handle the IACUC's business practices may make a change in previously approved animal numbers according to an existing IACUC policy without notifying the IACUC. Each institution that chooses to implement the guidance described in paragraph 3 of [NOT-OD-14-126](#) will need to integrate the policy into their operations. The institution may need to notify the office or individuals responsible for ordering and or housing animals, or for assigning animal holding space. It will be an institutional decision which individual(s), committee(s) or office(s) to notify. Note that the

institution is also responsible for developing and implementing a mechanism for recording the change in animal numbers in the protocol.

**C2:** Please change the wording in paragraph 2 ([NOT-OD-14-126](#)). Although the first sentence states that items 2.a.-2.c. *can* be handled administratively according to IACUC policies and with vet consultation, the sentences just before that list of items imply the opposite: “The veterinarian may refer any request to the IACUC... This includes changes in: ...” Perhaps moving those sentences to after items a-c, or leaving it in its current location but adding parentheses would make it less ambiguous.

**A2:** OLAW provides the following response to alleviate any confusion. The specific significant changes that may be handled administratively with veterinary consultation and verification according to IACUC-approved policies are described in 2.a. through 2.c. ([NOT-OD-14-126](#)). The remainder of the text in paragraph 2 describes specific details required in this method of administrative handling. (*The veterinarian is not conducting DMR, but is serving as a subject matter expert to verify that compliance with the IACUC-reviewed and -approved policy is appropriate for the animals in this circumstance. Consultation with the veterinarian must be documented. The veterinarian may refer any 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.*)

### **Veterinary Verification and Consultation of IACUC Policies**

**Q3:** If the approved protocol includes a range of doses for an analgesic agent, is veterinary review and verification of changes within that range required?

**A3:** No. OLAW and USDA encourage the use of appropriate ranges in protocols to encourage flexibility and reduce the likelihood of noncompliance by deviation from the IACUC-approved dose. If an IACUC-approved protocol includes a range of doses and the PI is within that range, there is no requirement for an amendment or for veterinary verification and consultation ([NOT-OD-14-126](#)).

**Q4:** If a range of doses was approved for a single analgesic agent, but the team now wants to change to different agent, would that be permitted?

**A4:** If a research team wants to change to an analgesic that is not listed on their protocol, and this change is permitted under an IACUC-approved policy, then that change would be permitted with veterinary verification and consultation ([NOT-OD-14-126](#)).

**Q5:** Is additional blood sampling and/or change in sampling time point considered a significant change? This sampling would be under the maximum limit of possible total volume allowed by IACUC policy in animals such as bovine, swine, and ovine.

**A5:** Yes, change in blood sample collection is a significant change. Additional blood sampling or changes in sampling time point would fall under paragraph 2.c. changes in duration, frequency, type, or number of procedures performed on an animal. These types of significant changes may be administratively handled in consultation with a veterinarian according to IACUC-reviewed and -approved policies as described in paragraph 2 of [NOT-OD-14-126](#).

**Q6:** Our IACUC opinion is that a blood sample collection does not cause elevated pain or distress and is momentary. Is this action considered significant because a needle stick causes pain and distress no matter the animal or its size?

**A6:** Blood collection is an animal activity that must be reviewed and approved by the IACUC; modification of previously approved blood collection procedures is a significant change. According to [NOT-OD-14-126](#), changes in duration, frequency, type, or number of procedures performed on an animal may be administratively handled according to IACUC-reviewed and -approved policies in consultation with a veterinarian as described in paragraph 2.

In response to your question, *is this action significant because a needle stick causes pain and distress?* No, this requirement is based on numerous factors. The IACUC may choose to include the following considerations in its policy on blood collection:

- species and size of the animal to be bled;
- estimated total blood volume of the animal;
- type of sample required (e.g., serum, whole cells);
- quality of sample required (e.g., sterility, tissue fluid contamination);
- quantity of blood required;
- frequency of sampling;
- blood values of the animal being bled (e.g., hematocrit and hemoglobin);
- training and experience of the phlebotomist; and
- effect of restraint on the blood parameter being measured.

## Documentation

**Q7:** If our IACUC elects to make use of administrative review for significant changes that are covered by an IACUC policy, do we need to update our Assurance with OLAW? If so, would we need to provide a copy of the IACUC policy providing authorization for some significant changes to be made to a protocol via veterinary administrative review?

**A7:** If your IACUC elects to make use of administrative handling of some significant changes that are covered by an IACUC policy, you may implement your policy(s) without immediate notification to OLAW. Institutions are expected to inform OLAW

of those program changes in the next annual report and when renewing the Animal Welfare Assurance. Institutions are NOT expected to attach copies of IACUC policies to the annual report or Assurance.

**Q8a:** What should take place following veterinary verification and consultation? Failure to have a specific policy for amending the protocol could lead to USDA citations when a protocol and research/medical records are not congruent.

**Q8b:** While the use of IACUC-approved policies with veterinary verification and consultation will reduce the administrative burden on the investigator for making modifications to approved protocols, shouldn't IACUCs have a specific policy on amending the protocol following such verification?

**A8:** IACUCs that choose to implement a process of administrative handling for some significant changes through veterinary verification and consultation must develop a process for documenting that verification and consultation ([NOT-OD-14-126](#)). The Notice states, *It is the IACUC's responsibility to clearly define and communicate its policy for determining significance to investigators.* This includes developing and implementing a policy for amending protocols following veterinary verification and consultation.

As stated on page 21 of this webinar transcript, *Documentation is required. We want to make sure that the change is available to the team working under the protocol and to the PI designing the next experiment or writing the next protocol. And also to the USDA VMO making an inspection visit. But keep in mind, we are doing this to reduce regulatory burden that we know is making it difficult for investigators to conduct their experiments and for IACUCs to meet their obligations. So OLAW and USDA want institutions to design a way to document the change that records the change in a useful way without being burdensome.*

### **The Scope of Guidance NOT-OD-14-126**

**C9:** On page 21 of this webinar transcript, you discuss the [AVMA Guidelines for the Euthanasia of Animals](#) (AVMA Guidelines) and indicate that AVMA-approved methods of euthanasia do not require scientific justification because the AVMA Guidelines are considered current practice standards. I do not think an IACUC should be approving methods of euthanasia that the AVMA panel has found to be unacceptable. I think what the IACUC may be asked to review and approve would be techniques not included in the AVMA list of approved techniques.

**A9:** The PHS Policy [IV.C.1.g.](#) allows the following: "Methods of euthanasia used will be consistent with the recommendations of the American Veterinary Medical Association (AVMA) Panel on Euthanasia, *unless a deviation is justified for scientific reasons* in writing by the investigator." The IACUC may approve methods proposed

by investigators that are outside AVMA-acceptable guidelines only with scientific justification that is satisfactory to the IACUC.

**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.

**Q11:** Prior to the NIH guidance [NOT-OD-14-126](#), was it allowed to have an IACUC policy to allow flexibility within a protocol?

**A11:** OLAW has always encouraged investigators to write flexibility and ranges into their protocols and IACUCs to approve such changes. [NOT-OD-14-126](#) extends this flexibility, permitting IACUCs to develop and approve policies regarding the implementation of some significant changes.

**Q12a:** What are the requirements for IACUC *approval* of policies?

**Q12b:** What is considered official action of the committee?

**A12:** By IACUC-approved policies, OLAW and USDA mean that the policies must be adopted by a formal action of the IACUC. Formal action of the IACUC falls into two categories. The first category is review and approval by FCR or DMR. The second is by polling the IACUC. Polling the IACUC could be done by telephone calls or email. Or, it could be done by posting the issue in an electronic format and having the IACUC members indicate their preference there. The important point is that the members of the IACUC are aware of the policies and accountable for the policies. (See this transcript page 4.)

**Q13:** Does the IACUC have to unanimously agree to approve IACUC policies?

**A13:** No. Concurrence of a simple majority of the IACUC is sufficient. If the IACUC chooses to approve policies at a convened meeting, a simple majority of the quorum may approve IACUC policies.

**Q14:** Regarding a change in animal numbers, if a revised rationale is required does this have to go back to the committee?

**A14:** The revision of the rationale for an administratively handled change in the number of animals used does not have to go back to the committee prior to the change in numbers being implemented. The PI may make the change in numbers according to the IACUC-approved policy. Then, if necessary, the rationale should be updated prior to the annual protocol review. OLAW and USDA anticipate that these changes in animal numbers will reflect refinements in the research. Updating the rationale for the numbers of animals used at the annual review will inform the IACUC and keep the protocol consistent with the ongoing activity.

**Q15:** According to [NOT-OD-14-126](#) paragraph 1.d., species changes require IACUC review, but what about strain changes within a species? Would a PI be allowed to change mouse strains as long as it didn't require IBC review as well? Or would a strain change require IACUC review?

**A15:** Changes in species must be reviewed and approved by the IACUC. Changes in strain do not require review or approval. All other reviews must be conducted as required, such as IBC review.

**Q16a:** If a PI is approved to perform a major survival surgical procedure on an animal and later determines that he or she needs to repeat the same surgical procedure on the animal, how should this modification be handled? Does it matter if the additional surgical procedure is survival or nonsurvival?

**A16a:** The addition of a major survival surgical procedure is a significant change that must be approved by FCR or DMR because the additional procedure may induce substantial pain or impairment to the animal. ([NOT-OD-14-126](#), [Guide](#) pages 30, 117) The additional survival surgery procedure must be essential to the research and scientifically justified (OLAW [FAQ F9](#)).

The addition of a major nonsurvival surgery in which the animal is euthanized before recovery from anesthesia is a significant change that may be handled administratively according to IACUC-reviewed and -approved policies in consultation with a veterinarian authorized by the IACUC.

**Q16b:** If a PI is approved to perform a minor surgical procedure and later determines that he or she needs to repeat the same minor surgical procedure on one of the animals, how should that change be handled?

**A16b:** A minor surgical procedure, by definition, causes little or no impairment to the animal with minimal or no complications. Therefore, repeating a minor surgical procedure is a significant change that may be handled administratively according to IACUC-reviewed and -approved policies in consultation with a veterinarian authorized by the IACUC ([NOT-OD-14-126](#) #2).

**Q17:** What is meant by changes *in housing and or use of animals in a location that is not part of the animal program overseen by the IACUC?*

**A17:** [NOT-OD-14-126](#) paragraph 1c says that a request to house an animal in a location that is not overseen by the IACUC is a significant change that must be reviewed and approved by the IACUC by FCR or DMR.

For example, IACUC approval by FCR or DMR must be granted to use animals:

- at a proposed satellite facility or proposed study area that has not been approved by the IACUC;
- at an animal facility of another institution; or
- at a location that is not reviewed by the IACUC as a part of the semiannual facility inspection (For additional information on IACUC semiannual inspection, see OLAW [FAQ E1.](#)).

Changes within locations that are overseen by the IACUC may be done according to the policies of the institution and the IACUC.

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