Jerald Silverman, DVM, Column Coordinator

Amendments for additional animals

Maurizio Marchetti's research involved understanding the evolutionary significance of biochemical pathways leading to different phenotypic expressions of drug metabolism. To help explain the type of research he did, he used the example that onions can cause a severe hemolytic anemia when consumed by dogs. "Why did that trait evolve?" Marchetti would say. "Dogs aren't pure meat-eaters; they eat all kinds of food. Why did they evolve having a toxic reaction to onions?" So it was not surprising for the Great Eastern University IACUC to see a protocol from Marchetti that included mice, dogs and rabbits. In fact, it was quite typical for Marchetti's research.

During the course of one of his studies, Marchetti was informed that he had used nearly all of the dogs that the IACUC had approved. The original approval was for 50 animals, which Marchetti had calculated to be adequate, but he realized now that he needed 5 additional dogs to complete his work. Because Great Eastern's policy allowed an increase in the number of animals of up to 10% to be considered a "minor amendment" to a protocol, Marchetti requested the five additional dogs using the school's minor amendment form. Unfortunately, he received a quick call from the Great Eastern IACUC office informing him that the school's approved Assurance to the U.S. Public Health Service (PHS) only allowed researchers to add up to 10% more rats or mice as a minor amendment. Adding dogs, or any other species, in any number required a major amendment and a standard IACUC review of the request. Amazed and confused, Marchetti pleaded his case to the IACUC chairman, Dr. Larry Covelli. Covelli reminded Marchetti that the PHS considered an increase in the approximate number of animals used to be a significant change that required IACUC review. "But that's the problem," said Marchetti, slowly losing his temper. "How can you and the PHS allow me to add 10% more mice as a minor amendment, but when I ask for the exact same percentage increase in dogs, it becomes a major amendment? What's the difference?"

"I'm sorry, Maurizio," said Covelli. "But when we went to renew our PHS Assurance, we were told to clarify that the 10% addition limit was for rats and mice, not dogs. So we did that, and it was approved. I know it will take a little longer, but you'll have to submit this as a major amendment."

What is your opinion? Should increases in animal numbers through minor amendments be limited to rats and mice, or should minor amendments also be used to add dogs and other large species?

RESPONSE

Not a minor amendment

Juan Jordán, DVM &
Karl Andrutis, DVM, MS, DACLAM

The Public Health Service *Policy on Humane Care and Use of Laboratory Animals* (PHS Policy)[1] and Animal Welfare Act and Regulations (AWARs)[2] require prior review and approval of significant changes to IACUC protocols; however, they have not defined all the changes that they consider significant. The National Institutes of Health Office of Laboratory Animal Welfare (NIH/OLAW)[3] suggests that each institution develop its own guidelines regarding significant protocol modifications and make these guidelines available to investigators to clarify the amendment process.

Many institutions allow some increase in animal number beyond that approved in the protocol to be considered a minor amendment. This is often 5–10% of the total number approved and is often limited to mice and rats. We have not found any regulatory justification for this institutional policy. Although allowing increases in animal numbers on a percentage basis does account in some way for the scale of the study, this can result in the addition of a substantial number of animals if the number of animals approved on the original protocol is large, as can be the case for mice and rats.

The PHS Policy and AWARs require that proposals to the IACUC specify and include a rationale for the approximate number of animals requested. These requirements include an implicit need for institutions to establish mechanisms for monitoring and documenting the number of animals acquired and used in approved activities. The PHS Policy (IV, C, 2)[1] and AWARs (S2.31, d, 2)[2] require the same review procedure for proposed significant changes in ongoing activities (protocols) as they do for new activities. NIH/OLAW[3] goes further to list as an example of a significant change any change "in the species or in approximate number of animals used."

To comply with NIH/OLAW guidance, we believe that the addition of animals of any species (mice, rats or USDA-covered species), irrespective of the number, is not a minor amendment and requires designated or full committee review, as the institution's policies dictate. It is important to keep in mind that the mechanism adopted by the institution to add animals must satisfy the PHS Policy requirement that the number of animals approved be limited to the number needed to obtain valid results[4].

1. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).
2. Animal Welfare Act and Regulations.
3. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* – Frequently Asked Questions (US Department of Health and