

Jerald Silverman, DVM, Column Coordinator

Going through the phases

Best America Pharmaceuticals was an NIH/OLAW-Assured institution. Dr. Joy Holmes of Best America studied diseases of the pancreas. In a preliminary test with a very small number of rats, a new compound, P20R, was found to cause pancreatic damage similar to what she had sought for many years for her research. Consequently, in her IACUC application, Holmes proposed an initial ‘up and down’ acute oral toxicity test with P20R to calculate an estimate of its lethal dose for 50% of the rats (LD_{50}). On her application, she called this test Phase I. Once Phase I was completed, she proposed Phase II, a larger study with 50 rats. Using the information from Phase I, Phase II would determine the dose and frequency of use of P20R that would cause pancreatic lesions in approximately 90% of her rats (ED_{90}). The final part of her study, Phase III, would use the results of Phase II in conjunction

with her ongoing studies pertaining to the treatment of pancreatic injury. For Phase III, 500 rats were requested; however, her protocol stated that if an ED_{90} could not be established in Phase II, the project would be terminated. Holmes clearly justified the number of animals she would need for all three phases of her study, and the IACUC was satisfied with the significance of the study and all aspects of animal care and use.

The primary question facing the IACUC was whether to approve the entire study as requested by Holmes or to wait until the two earlier testing phases were completed before releasing the animals for Phase III. The researchers on the committee wanted to approve the entire study because, they said, Holmes was required to follow her protocol: if Phase II did not provide the needed ED_{90} , she was obligated not to use the remaining animals, even if they had been approved

for potential use. As one member put it, “The entire IACUC system is based on self-regulation, and if we can’t trust Joy Holmes to do what she said she will do, why do we even have an IACUC?” Others on the committee felt differently. For example, one said, “The IACUC is based on self-regulation by our company as a whole; it’s not focused on any one person. If everybody always did the right thing—which is naïve thinking—only then would there be no need for an IACUC.” Those members wanted to release the 500 rats for Phase III only if Phase II was reported to the IACUC as being successful. A third group wanted Phase III to be a separate protocol or a major amendment to the existing protocol if Phase II was successful.

If you were a member of the Best America IACUC, how would you approach approving the requested number of animals in Holmes’ protocol?

RESPONSE

Post-approval monitoring

Jake Bair, BS

It is important for IACUCs to carry out thorough reviews of protocols and equally important for them to implement good animal use monitoring systems. By monitoring a protocol, an IACUC can make sure the protocol is being carried out as it was approved. The Animal Welfare Act¹ requires IACUCs to conduct continuing reviews of activities involving animals at intervals determined by the IACUC but not less than annually. Monitoring of animal care and use is required by OLAW². However, neither the Public Health Safety *Policy on Humane Care and Use of Laboratory Animals*³ nor the *Guide for the Care and Use of Laboratory Animals*⁴ specifically addresses a requirement for post-approval monitoring procedures to compare actual study activities with the

description in a protocol. The main charge of an IACUC is to oversee the animal care and use program, which includes reviewing protocols, evaluating programs, reporting noncompliance, ensuring that individuals working with animals are properly qualified and trained, and responding to concerns about animal care and use.

Each member of the Best America IACUC is responsible for overseeing and monitoring Holmes’ study protocol. How can this be accomplished? The Best America IACUC should rely on a well established veterinary program to provide an additional level of monitoring. The authority and responsibility for animal activities are delegated to the veterinarian and animal care staff. This team of trained individuals observes animals daily, provides post-operative animal care, evaluates outcomes of procedures by principal investigators and reports incidents that may involve occupational health and safety as appropriate. The veterinarian supervises

the aforementioned activities, follows up with animal concerns voiced by animal care staff and provides hands-on training in animal procedures. The animal care staff may choose to implement a post-approval monitoring system to provide an additional level of monitoring for procedures and practices associated with Holmes’ study.

With an appropriate veterinary program in place at their institution, the members of Best America’s IACUC should approve the entire study protocol with the provision that Holmes must report the results of each phase of her study to the IACUC. The IACUC would then approve the release of additional rats for each subsequent phase of the study on the basis of her reported results. This would allow the IACUC to monitor the study and ensure that the protocol is being carried out as it was approved. In addition, Best America’s IACUC could require the veterinary program to implement a post-approval monitoring program to observe different